Multicenter Evaluation of the Glucometer Elite XL Meter, an Instrument Specifically Designed for Use With Neonates

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OBJECTIVE — To evaluate the clinical performance of the Glucometer Elite XL Diabetes Care System in neonatal settings using a multicenter study.

RESEARCH DESIGN AND METHODS — A total of 388 blood specimens from 333 neonates were included in the study. A capillary or arterial sample was analyzed for determination of glucose with the Glucometer Elite XL system by an attending trained nurse. Through the same sampling site, a specimen was collected and sent to the laboratory for measurement of plasma glucose, bilirubin, and hematocrit.

RESULTS — The regression analysis between the results of the Glucometer Elite XL system and comparative methods resulted in the following: Glucometer Elite XL meter = 1.01 × laboratory method + 0.02 mmol/l (n = 388). For the 1.1–4.0 mmol/l plasma glucose range, the regression was Glucometer Elite XL meter = 1.07 × laboratory method + 0.12 mmol/l (n = 150). A difference plot indicated a mean bias of 0.04 mmol/l (95% CI −0.01 to 0.10). No relationship was found between meter glucose biases and hematocrit levels (r = 0.10, P = 0.14). Although a statistically significant correlation existed between bilirubin levels and the glucose meter biases (r = 0.14, P = 0.005), the predicted mean biases were of little clinical significance.

CONCLUSIONS — The Glucometer Elite XL system showed a good performance when used in neonatal settings.

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Blood glucose meters are widely used in point-of-care testing (POCT). They are also used by diabetic patients as a major tool for managing their disease. Many studies have shown that blood glucose meters are sensitive and accurate when used in an adult population (1–3). In a recent study, Jeffrey et al. (4) evaluated the performance of 5 blood glucose meters and concluded that all meters satisfied their criteria for POCT. However, the use of these devices in neonatal settings where hypoglycemia and variable hematocrit levels are concerns has not given satisfying results until now. Kirkham and Watkins (5) evaluated 2 reflectance photometers and concluded that these instruments gave unpredictable results and should be used with caution in neonatal units. Two articles (6,7) showed that blood glucose meters gave inaccurate results when hypoglycemia was present in neonates and therefore were not adequate devices for use in neonatal settings. In a short report, Kilpatrick et al. (8) showed that some meters exhibit variations in accuracy with various hematocrit levels. The necessity to rely on the laboratory to confirm results with existing systems has prompted manufacturers to develop new systems to overcome this problem. Nevertheless, a pressing need exists for instruments that require only microliters of whole blood to obtain results within 20–60 s in neonatal settings. The use of these devices would save time in the monitoring of neonatal hypoglycemia and would improve care.

The Glucometer Elite XL Diabetes Care System (Bayer, Tarrytown, NY) is a blood glucose meter designed to monitor plasma glucose in neonatal settings. However, it can also be used for diabetes management in adult populations just like the Glucometer Elite system currently on the market. The plasma glucose measurement range is from 1.1 to 33.3 mmol/l. The Glucometer Elite XL system gives results within 30 s and is calibrated to provide blood glucose results equivalent to laboratory plasma and serum glucose methods on the market. The method is based on electron-mediated oxidase chemistry. The required volume for a plasma glucose determination is ~3 µl.

The purpose of this study was to compare the performance of the Glucometer Elite XL system in neonates with a laboratory method through a multicenter study. The potential interference of bilirubin and hematocrit on the plasma glucose results was evaluated.

RESEARCH DESIGN AND METHODS

— This multicenter study was conducted in 4 neonatal units in North America (Quebec City, Quebec, Canada; Winnipeg, Manitoba, Canada; Minneapolis, MN; and Indianapolis, IN) and lasted ~8 months (from August 1998 to April 1999). The institutional review board or

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Abbreviations: PCOT, point-of-care testing.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

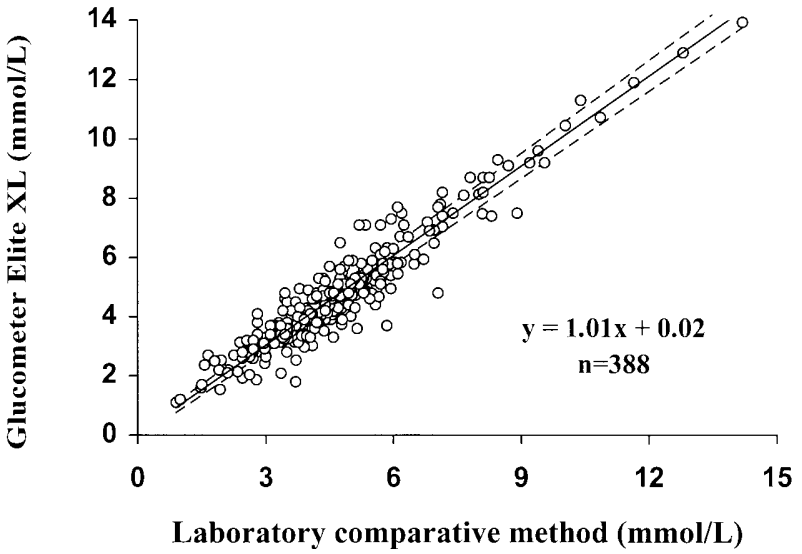

Figure 1—*Passing-Bablok regression of the results from the Glucometer Elite XL system and those obtained with the laboratory comparative methods. – – –, 95% CI of the slope.*

ethics committee at each site approved the study. Collaborators assigned to the project (mostly nurses and laboratory technologists) were trained before the beginning of the study. They were taught to use the Glucometer Elite XL system, and each of them performed triplicate assays of the glucose control solutions (low, normal, and high) to familiarize themselves with the meter, reagents, and proper testing technique.

Meter operators performed glucose measurements using control solutions (in duplicate) each day that they performed a plasma glucose measurement on a neonate. Also, electronic components of the meter were tested each day using the Check Strip (Bayer). One lot of test strips was used for the entire study.

The laboratory comparative methods were assessed for precision and accuracy. Six levels of serum glucose control samples with glucose concentrations determined using the Centers for Disease Control and Prevention/National Institute for Standards and Technology hexokinase reference method for glucose (9) were analyzed (in duplicate) before the study and once each week thereafter. Accuracy was defined as ±5% of the target glucose level, and precision was defined as ±5% of the difference between replicates. Also, routine quality control data for each laboratory were checked each week.

Newborns were included in the study after written consent was obtained from one or both parents when required by the site institutional review board or ethics committee. The infants were included only if a blood specimen was to be drawn during the course of their normal medical care. When a sample was taken for routine medical care (by capillary puncture or through an indwelling catheter), the attending nurse performed a plasma glucose measurement with the Glucometer Elite XL system and collected an additional 400–500 µl of whole blood in a heparin-lithium microcollection container (Microtainer; Becton Dickinson, Rutherford, NJ) for laboratory glucose (in duplicate) and total bilirubin determinations. The specimens were centrifuged immediately in the nursery or kept on ice water during transport to the laboratory to restrict glucose utilization by blood cells. A sample was also collected for a hematocrit determination using a microcapillary tube and a StatSpin microcentrifuge (StatSpin Technologies, Norwood, MA). For plasma glucose measurement in the laboratory, 3 sites used a hexokinase method, and 1 site used a glucose oxidase method. The laboratory comparative methods were considered to have no interference from bilirubin or hematocrit.

Agreement between methods was verified using a Passing-Bablok regression (10) of Glucometer Elite XL system and laboratory results. The Passing-Bablok regression does not assume that the reference method is free of imprecision and that the distribution of the differences between the methods is constant for all studied concentrations (homoscedasticity). This nonparametric regression is therefore more appropriate than least-squares regression in method comparison studies. The slope and *y*-intercept were tested for a significant difference from 1 and 0, respectively, using a $P < 0.05$ significance level. To evaluate the risk of missing clinically significant hypoglycemia, we calculated the probability of missing a plasma glucose level <2.2 mmol/l if a threshold of <3.0 mmol/l is used as an indication for control with the laboratory method.

RESULTS — A total of 388 samples were collected from the 4 sites. The age of the newborns when they entered the study ranged from 0 to 83 days (75th percentile = 5 days), and the week of gestation ranged from 23 to 42 (75th percentile = 40 weeks). The specimens included 200 specimens from neonatal intensive care units and 188 specimens from routine or well-baby neonatal units. Birth weight varied from 511 to 5,448 g.

Plasma glucose results varied from 1.1 to 13.9 mmol/l, hematocrit results varied from 24 to 82%, and total bilirubin results varied from 0 to 563 µmol/l. The mean bias between plasma glucose results from the Glucometer Elite XL system and the laboratory comparative method was 0.04 mmol/l (95% CI −0.01 to 0.10). Using a relative difference of 20% at plasma glucose levels >5.5 mmol/l or an absolute difference of 0.83 mmol/l at plasma glucose levels <5.5 mmol/l, 90.2% of the plasma glucose results were within desirable limits. These limits are those recommended by the National Committee for Clinical Laboratory Standards (NCCLS) (11). A Passing-Bablok regression resulted in the following: Glucometer Elite XL meter = 1.01 × laboratory method + 0.02 mmol/l (n = 388) (Fig. 1). The 95% CI of the slope was 0.98–1.04 and was not significantly different from 1. Because neonates generally have lower plasma glucose values than adults, the regression of plasma glucose results <4.0 mmol/l was assessed. The following was obtained: Glucometer Elite XL meter = 1.07 laboratory method + 0.12 mmol/l (n = 150) (Fig. 2).

When considering the CIs of the bias between the blood glucose meter and the laboratory measurements, a 2.5% risk of missing a plasma glucose level <2.2 mmol/l exists only if results <3 mmol/l are controlled. There is a 1% risk of missing a plasma glucose level <1.8 mmol/l using the same threshold for controlling with the laboratory.

Possible interference from hematocrit or bilirubin on the plasma glucose mea-

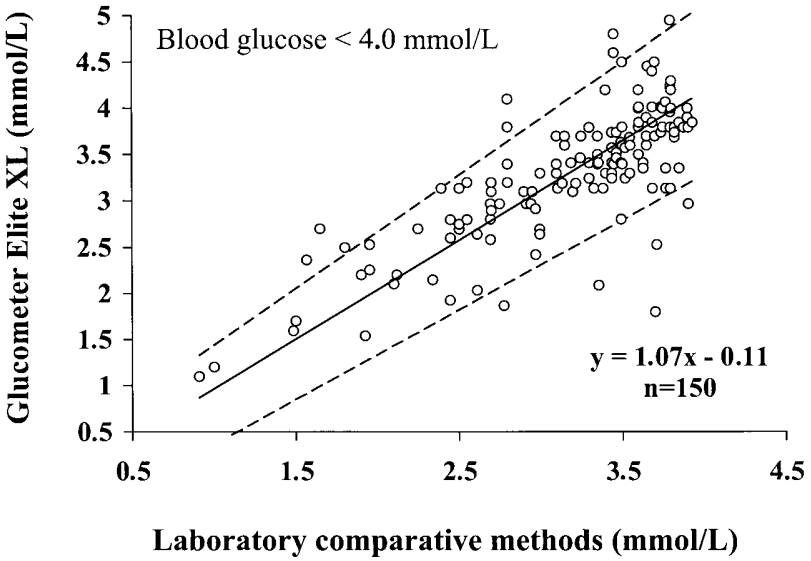

Figure 2—*Passing-Bablok regression of the results from the Glucometer Elite XL system and those obtained with the laboratory comparative methods for plasma glucose values <4 mmol/l. – – –, 95% CI of the slope.*

surement with the Glucometer Elite XL system was evaluated. Assuming the laboratory method had no interference from hematocrit, a plot of the hematocrit values as a function of the difference between the laboratory methods and blood glucose meter results was made (Fig. 3). A negative slope of 0.0041 (not significantly different from 0) was obtained ($P = 0.14$). For bilirubin, a similar comparison was plotted (Fig. 4) and gave a negative slope of 0.001 that was significantly different from 0 ($P = 0.005$). However, if only the total bilirubin results of <300 µmol/l were examined, then the slope was not different from 0 (data not shown).

CONCLUSIONS — This multicenter study evaluated the performance of the Glucometer Elite XL system at 4 neonatal units in North America by comparing the results obtained with this portable instrument with those of the laboratory method at each site. Few articles have been published that evaluate glucometer use on neonates, and the results have been less than satisfactory (5,6). The normal blood glucose level of neonates is lower than that of adults and is generally <4.0 mmol/l (12). Also, neonates are at risk for hypoglycemia. Some investigators have reported that hypoglycemia is encountered in up to 20% of the neonatal population (12,13). Therefore, a blood glucose meter should give accurate results in the 1.0–4.0 mmol/l range to be a useful instrument in a neonatal setting.

A neonate with a plasma glucose level <2.2 mmol/l is generally considered to be hypoglycemic. However, a level as low as 1.4 mmol/l without clinical symptoms is associated with a good prognosis. Most neonates return to euglycemic levels within 2 h, even if they have plasma glucose levels between 1.4 and 2.2 mmol/l at 1 h postpartum (12,14). To eliminate the risk of missing clinically significant hypoglycemia, all values <3 mmol/l should be controlled with the laboratory method. Approximately 10% of the glucose levels measured in one of the participating intensive neonatal care units (St. François d'Assise 1999 statistics, $n = 4,452$) were <3 mmol/l. Thus, the need to take a higher blood volume from most neonates would be eliminated.

We used the Passing-Bablok regression to evaluate the agreement between methods. This nonparametric method assumes that both methods involve analytical errors (10). This regression method does not allow the calculation of a regression coefficient. However, the correlation coefficient calculated using least-squares regression is very sensitive to the range of values included in the comparison. One or 2 high values can significantly increase the correlation coefficient without changing the agreement between methods. Moreover, 2 different methods can show a perfect correlation coefficient ($r = 1$) but have a significant systematic bias between them (15).

A good correlation between the Glucometer Elite XL system and the laboratory comparative methods was obtained in this study. The 95% CIs included the value 1 for the slope and the value 0 for the *y*-intercept, which indicates that the studied method was acceptable as an estimate of the laboratory method. The same regression was applied to the 150 plasma glucose results that were <4.0 mmol/l. Although the regression line gave a slope and *y*-intercept that were not as close to the goal of 1 and 0 as the first one, no significant differences were detected for these 2 parameters.

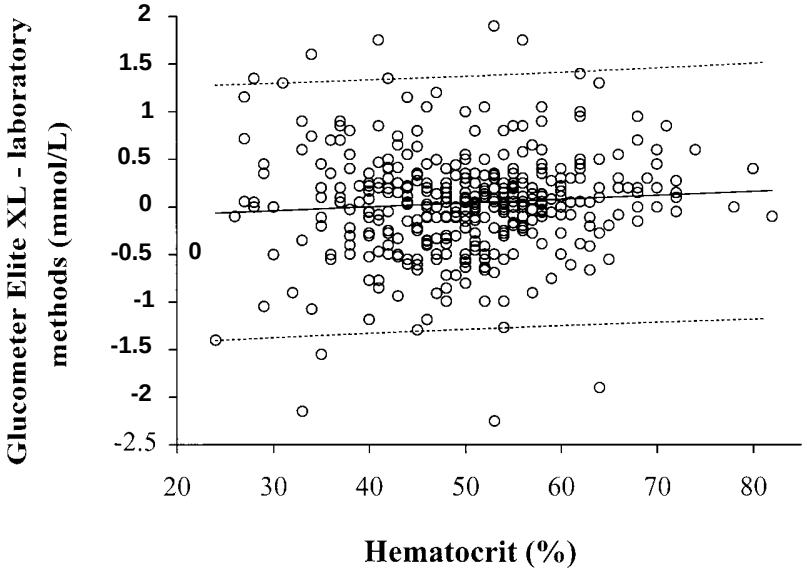

Figure 3—*Effect of hematocrit on plasma glucose differences between the results from the Glucometer Elite XL system and those of the laboratory comparative methods. – – –, 95% limits of agreement.*

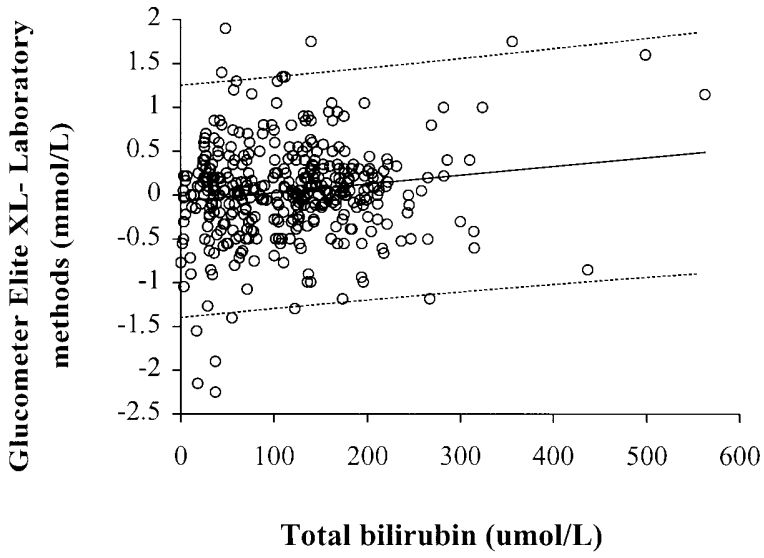

Figure 4—*Effect of bilirubin on plasma glucose differences between the results from the Glucometer Elite XL system and those of the laboratory comparative methods. – – –, 95% limits of agreement.*

Some manufacturers have limited the range of safe hematocrit levels to between 0.25 to 0.60% for the measurement of plasma glucose with a portable instrument. We have tested the influence of hematocrit for the range of values generally expected in neonates (16). At least 3 articles (7,17,18) demonstrated that hematocrit could influence plasma glucose measurement with some meters. According to these authors, high levels of hematocrit were associated with underestimation of glucose results, and lower levels of hematocrit were associated with overestimation of glucose results. The range of hematocrit studied in these articles was from 15 to 60%. However, a more recent article (19) studied the same range of hematocrit and did not find any interference. The new Glucometer Elite XL system had the capability of providing accurate results for specimens with high or low hematocrit levels as demonstrated in this study.

Few articles have evaluated the effect of bilirubin on plasma glucose measurement in POCT. Kiyoyasu et al. (20) found no interference but limited their study to a maximum bilirubin level of 24 μmol/l. Also, Duly et al. (21) reported that bilirubin levels up to 510 μmol/l had no significant effect on plasma glucose measured with a blood glucose meter. However, the authors obtained a maximum difference in mean plasma glucose of 0.6 mmol/l at 2.9 mmol/l (21%). Our results showed a slope significantly different from 0 when all bilirubin values were considered, but no more than 10 samples gave results >300 μmol/l. When these results were excluded from the regression, the slope was not significantly different from 1 (data not shown). Nevertheless, these data suggest that plasma glucose results obtained in neonates with high bilirubin concentrations should be controlled with a laboratory method if a difference of 0.3–0.4 mmol/l would change clinical management (i.e., borderline normal results).

Although this study was conducted in large hospital centers, the results can be generalized to any establishment where the staff members performing PCOT are adequately trained. Nurses or technologists performed the plasma glucose measurements during routine care. The additional control specimen runs were used to document instrument imprecision rather than to achieve a better performance. The volume needed by the blood glucose meter (3 μl) is much lower than what is necessary for the conventional laboratory method (200–250 μl). Provided that the operator waits for the blood glucose meter audio signal, the meter has little risk of falsely low results. If all results <3 mmol/l are controlled, then these false results would be easily recognized.

In conclusion, our results show a good correlation between the Glucometer Elite XL system and the laboratory comparative method for the measurement of plasma glucose in neonates. No interference from hematocrit was detected, but users should pay attention to specimens with bilirubin levels >300 μmol/l if hypoglycemia is a concern and the results are borderline normal. Only ~10% of the plasma glucose determinations in neonatal units that are <3 mmol/l would need to be controlled with the laboratory method. The Glucometer Elite XL system can be helpful in neonatal settings for the screening of hypoglycemia in most cases.

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