Assessing the quality of Bionime self-monitoring blood glucose system Rightest GM110: A critical evaluation of interference and ambient circumstances
Cheng-Teng Hsu, Hung-Chan Hsiao, Ming-Shih Lee, Shuo-Fen Chang, Tsung-Chien Lee, Yang-Sheng Tsai, Jyh-Myng Zen

Abstract
Background: The key issue in preventing chronic diabetic complications is to maintain near-normoglycemia. Analytical evaluation of Bionime self-monitoring blood glucose (SMBG) Rightest GM110 was carried out in this study.
Methods: The evaluation was executed according to the Standards for Reporting Diagnostic Accuracy (STARD) and the Clinical and Laboratory Standards Institute (CLSI). The evaluation procedure mainly focused on analytical performance. The accuracy tests included hematocrit, interferants, temperature, humidity, altitude and clinical evaluations.
Results: Good linearity response (R2N0.99) and satisfactory precision (CVs: 1.1 – 2.8%) were observed in glucose concentrations of 0.6 – 30.5 mmol/l. In hematocrit test, the Rightest GM110 was suitable for use in sample containing hematocrit in the range of 30 – 55%. Interfering test indicated that almost all substances tested were insignificant, with bias b10% in medium- and hyper-glycemia samples. Satisfactory stability was also found under various ambient circumstances, with bias within ±10%. In clinical trials, values within the acceptable zone (A+B) were 100% and values within zone A exceed 95% in error grid analysis.
Conclusions: The Bionime Rightest GM110 is reliable to display accurate glucose concentrations in specimens with irresistible interfering factors.
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ABSTRACT

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Results: Good linearity response (R²>0.99) and satisfactory precision (CVs: 11–2.8%) were observed in glucose concentrations of 0.6–36.5 mmol/l. In hematocrit test, the Rightest GM110 was suitable for use in sample containing hematocrit in the range of 30–55%. Interfering test indicated that almost all substances tested were insignificant, with bias <10% in medium- and hyper-glycemia samples. Satisfactory stability was also found under various ambient circumstances, with bias within ±10%. In clinical trials, values within the acceptable zone (A+B) were 100% and values within zone A exceed 95% in error grid analysis.

Conclusions: The Bionime Rightest GM110 is reliable to display accurate glucose concentrations in specimens with irreducible interfering factors.

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1. Introduction

Glucose monitors, when used in conjunction with appropriate interventional treatment, can effectively improve glycemic control [1]. The US Food and Drug Administration (FDA) has approved more than 200 glucose monitors for home and institutional use by carefully reviewing clinical and laboratory evidences provided by device manufacturers [2,3]. Devices should be evaluated prior to clinical use in order to ensure that the results are sufficiently reliable for medical treatment [4]. Although protocol guidelines are available, a standardized approach for this type of evaluation is necessary [5].

It is difficult to prove the accuracy of glucose monitor and the test must be carefully executed in order to minimize experimental error [6]. The blood glucose level determined by self-monitoring blood glucose (SMBG) influences how a patient is managed [7]. Unfortunately, different glucose meters usually result in different blood glucose concentration. A recently published report shows that many evaluations of glucose monitor performance do not conform to quality guidelines for protocol design or result coverage [3]. Therefore, in some cases that use the same monitor, conflict evaluations were published by clinicians [8–11]. This inconsistency can even cause a confusion to hinder new development in glucose monitors [3].

Total error (analytical plus user error) must be considered in the evaluation of any analytical device. Analytical imprecision and bias are controlled by testing products that conform to specifications, and such good or poor performance is attributed to device manufacturers. The user error mainly derives from random patients' interferences [12]. There are many physiological differences between blood samples, such as hematocrit (Hct), endogenous secretions, and exogenous additives. Many studies report the effect of Hct on glucose monitoring systems [13,14]. Clinician should also be aware of the possible interference from saccharides, such as maltose, iodocetin, galactose, and xylose, to interfere with blood glucose monitoring systems using test strips that contain GDH-PQQ or glucose dye oxidase [15,16]. Physicians and professional organizations have thus been warned

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Abbreviations: SMBG, self-monitoring of blood glucose; Hct, hematocrit; STARD, Standards for Reporting Diagnostic Accuracy; CLSI, Clinical and Laboratory Standards Institute.

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Table 1
A table of total 22 factors: test concentrations and solvents

<table>
<thead>
<tr>
<th>Item</th>
<th>Interferent</th>
<th>Solvent</th>
<th>Test conc.</th>
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<tbody>
<tr>
<td>Erythrocytes</td>
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| Hct interference was studied using venous samples. All samples were spun down to separate erythrocytes from plasma. Plasma and erythrocytes were then mixed to achieve various Hct levels in the range of 20 to 70% as measured by capillary tube. Each mixed completely samples were tested with 3 target plasma glucose concentrations (hypoglycemia: 2.2–3.8 mmol/l, medium glycemia: 6.1–11.1 mmol/l, and hyperglycemia: 16.0–25.0 mmol/l), as measured with the comparison reference). Each sample was analyzed in 5 replicates with the glucose meter. Samples were analyzed within 10 min after mixing to avoid significant glycosis. The criteria recommended are: all bias (vs. comparison methods) is within ±20% interval.

2.4. Interference analysis

In total, 24 factors including exogenous and endogenous substances, anesicongen, anticonvulsants, and microbiotics were used to assay effects of interference in the range of 3.8–6.1 and 13.6–22.0 mmol/l glucose concentration: samples. The criteria recommended are: bias (vs. comparison method) is within ±20% interval. The studied interferents and their concentrations were shown in Table 1. Some drugs are supplied by Chung Shan Medical University Hospital (Taichung, Taiwan). The potential for interferences by cholesterol and uric acid were also tested.

2.5. Assessment of ambient circumstances

Three ambient circumstances including temperature, humidity and altitude were analyzed. Control solutions were used as test samples. The criteria recommended are: each bias (vs. comparison method) is within ±10% interval for medium- and hyperglycemic control solutions. The range of 10–40°C temperature was tested under relative humidity of 40%. The test takes 25°C as a basis of comparison reference. The humidity test was analyzed at range of 50% humidity under a temperature of 23 ± 5°C. Relative humidity of 10% under a temperature of 23 ± 5°C was used as comparison reference. The range of 0–3000 m altitude to see level was analyzed. The altitude test took sea level as a basis of comparison reference.

2.6. Statistical and clinical evaluation

In total 164 patients, diabetics and non-diabetics, enrolled in clinical trials at the outpatient clinic of Chung Shan Medical University Hospital. The clinical trial evaluated performance of the Biomine SMBG system Righstem GM110. The age range of the 164 volunteers (55 males and 109 females) was 21–85 y (mean: 48.7±16.3 y). Subjects were not necessarily users of the Biomine Righstem meters, informed consent was obtained from each participant and the study protocol was reviewed and approved by the clinical trial committee of Chung Shan Medical University Hospital for evaluation involving human subjects (IRB Authority No. CS0787).

Clinical accuracy was tested through comparison between glucose meters and comparison method: Olympus AU40. Three alternative sites, including finger tip, palm, forearm, were evaluated simultaneously. Two methods, i.e., linear regression analysis and Clarke Error Grid Analysis (EGA), were adopted in this analysis [28]. Clinical acceptability of the results was evaluated using Clarke EGA. For this analysis, the capillary glucose results obtained with the meter were plotted in comparison with plasma glucose from Olympus AU40. We used the hexokinase method on an Olympus AU40 instrument (Olympus America) as a comparison method. The resulting data points were categorized into zones according to the clinical severity of the risk for the measurement error while correlations were determined by linear regression. In addition, each specimen was tested simultaneously for cholesterol and uric acid concentrations by Olympus AU40 and analyzed for their effect of interference on glucose monitoring.
3. Results

The Biothree Rightest GM110 meter showed excellent linearity ($R^2>0.99$) over the tested range of 0.6–30.5 mmol/l (10–549 mg/dl). As shown in Fig. 1, the meter displayed Lo or Hi signal when glucose concentration was <0.6 mmol/l or >33.3 mmol/l, respectively. Furthermore, the glucose monitoring system showed satisfactory within-run precision, CVs=1.1–2.8% in the range of 2.3–16.6 mmol/l glucose concentrations of venous blood samples (data not shown).

The marketed glucose monitoring systems are required to be suitable for use in extra-low Hct neonatal samples and extra-high Hct samples. In this study, accuracy of Rightest GM110 (bias=10%) was satisfactory in the range of 30–55% Hct of samples (data not shown). It was surprising that 20–70% Hct samples in 3 glycemic levels were all within defined criteria, suggesting that it is acceptable for use in neonatal and extreme Hct samples.

There are other factors especially in critically ill patients that influence biosensor measurements and thereby contribute to bias between results measured by glucose meters and those from comparison method. In total, 24 kinds of substances were assessed in the evaluation procedures according to CLSI EP7-A2 statements [25]. As shown in Fig. 2, no substance caused significant interference (absolute bias >20%) on glucose measurements with the glucose oxidase-based Rightest GM110 meter. Since critically ill patients represent a significant group for whom self-monitoring of blood glucose is desirable, we would therefore anticipate that the proposed meter/strip system can be used for these patients (Fig. 2).

In clinical trial, Fig. 3 shows the results of EGA. The meter had 97.0% (158/164) of values in acceptable zone A and 5 values in acceptable zone B. The results of fingerstick tests were similar to that of palmstick and armstick tests indicating that Rightest GM110 meter was clinically acceptable for alternative sites. Note that physiologically normal ranges for uric acid and cholesterol are 0.1–0.4 mmol/l and 3.6–5.2 mmol/l, respectively. In clinical trial, it was shown that there was no significant correlation between glucose measurements bias and uric acid concentrations for Rightest GM110 meters, the satisfactory result was also seen in cholesterol analysis (cholesterol test: $y=-1.3663x+7.5618$, $R^2=0.0308$; uric acid test: $y=-0.7536x+0.7112$, $R^2=0.0001$) (Fig. 4). This study showed that cholesterol and uric acid did no significant effect on glucose measurements using Rightest GM110 meter even outside physiologically normal range.

The assessment of environmental circumstances also showed acceptable stability under various ambient circumstances. As can be seen in Fig. 5, the bias was in the range of −1.9 to 0.7% for medium-glycemic range of control solution and in the range of −1.0 to 2.2% for hyper-glycemic control solution in humidity test. Similar results were observed at these various temperature conditions, i.e., the bias was in the range of −5.0 to 3.0% for medium-glycemic control solution and in the range of −5.4 to 6.7% for hyper-glycemic control solution. These results were all within defined criteria. Finally, the altitude test also

Fig. 2. The interference tests of 24 kinds of physiological factors on glucose measurements. The effect of interference is expressed as bias between results of an excess of factors and comparison method results. The black bars represent medium-glycemic range of specimen and open bars represent hyper-glycemic range of specimen.

Fig. 3. Error grid analysis (EGA) for finger tip blood glucose results using Biothree Rightest GM110 compared with venous plasma glucose values obtained from the Olympus AU640. Total specimens, N=164.

Fig. 4. The effect of (a) cholesterol and (b) uric acid on glucose monitoring in clinical trial.

proved acceptable performance of glucose measurements with bias of within ±2% interval at various ranges of altitude.

4. Discussion

The SMBG system, Bionime Rightest GM110 meter, demonstrates that the glucose meter's analytical range should cover glucose concentrations from 1.1 to 33.3 mmol/L to meet glucose concentration variations. Yet, many glucose meters cannot meet this requirement. The linear regression equation, 0.966 x + 0.040 (Plasma value) - 0.34 mmol/L, in glucose concentrations of 1.1-33.3 mmol/L for Bionime Rightest GM110 is in good correlation and agreement with comparative plasma glucose measurements.

The satisfactory imprecision of the commercially available SMBG systems under controlled laboratory conditions is 2–5% [25,30]. The within-run and between-run precision tests demonstrate that the CVs are <3%, indicating that Bionime Rightest GM110 has a better meter/strips variation. The imprecision of glucose measurements is attributed to inconsistency of the electrochemical response area [31] and efficient control of the electrochemical area are considered an effective improvement in precision and can achieve through a simplified fabrication technique of the GM110 [19,20,32].

The American Diabetes Association (ADA) recommends control of all glucose meters both at the start of usage and at regular intervals thereafter [33]. The approach of such control is to compare values of near patients devices measurement with those of laboratory values [34]. Up to now, multiple performance goals have been proposed for glucose meters. The American Diabetes Association suggests an analytical goal of <5% [35]. The CLIA 88 guideline states that results should be within 10% or 0.3 mmol/L of target [36,37]. ISO 15197:2003 documents [27] request that 95% of values for the meters under evaluation should fall within ±0.83 mmol/L interval at glucose concentration <4.2 mmol/L and within ±2% interval at glucose concentration ≥4.2 mmol/L. In comparison to the reference, the Bionime Rightest GM110 yields a mean absolute error of 6.2%. This only exceeds the glucose meter error of 5% recommended by ADA slightly but still meets the analytical quality goals of CLSI and ISO 15197:2003. An alternative approach to total error assessment is ECA, with a scattergram of results classified into zones, such as A–E. This study shows that Bionime Rightest GM110 produces clinically acceptable results.

Many factors including variations in Hct, altitude, blood pressure, oxygen tension, endogenous factors of specimens, ambient temperature, humidity, and so forth may influence the accuracy results of whole blood glucose measurements [38]. The Rightest GM110 has a satisfactory performance concerning Hct-related effects on the accuracy of measurements within the manufacturer-suggested Hct range (30–55%). In clinical trial, the effect of Hct was minimized by the exclusion of samples with Hct values outside the range of 30–55%. There are still other factors that can influence the accuracy of glucose monitoring meter/strip systems. Unfilled completely strip is one of such factors while excessive time delay between meter and comparison method is another possible influencing factor. In view of the possible decline of blood glucose concentration with time after collection, capillary whole blood specimens were tested within 5 min of collection. Venous samples were collected with heparin-containing tubes and plasma glucose concentrations were measured within 60 min of collection at the same time, consistent with the standards recommended by CLSI. This study indicates that commonly used anticoagulants show no significant effect on the accuracy of glucose measurements using the Rightest GM110 meters. The Bionime Rightest GM110 meter is thus suitable for use in non-ideal ambient circumstances.

In conclusion, ambient temperature, humidity, and altitude have no significant effect on the Rightest GM110 meter reading for all categories of glucose concentration. The effect of all 26 interferents on the accuracy of Rightest GM110 meter is insignificant. The Bionime Rightest GM110 can provide clinically accurate and precise results for glucose monitoring in capillary whole blood samples for alternative site tests. Both clinical and analytical evaluations are satisfactory in providing a global assessment of Bionime Rightest GM110 in terms of its use in clinical setting.

Appendix A. Supplementary data


References


