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Original Article

Analytical Performance and Quality Control of a Glucose Monitor System

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ABSTRACT

Background and Objective: **The reliability and validity of monitors for self-monitoring of blood glucose are debated. We evaluated the analytical performance of Accu-check Active (Boehringer Mannheim, Roche) which is one of the most commonly used monitors in Iran.**

Material and Methods: **We compared the monitor readings with the reference values by percentage of values within certain intervals of the reference method, regression analysis, and difference plot. We used operational process specification charts to determine the probability that different QC rules would detect an analytical error. In addition, we assessed the quality on the sigma scale.**

Results: **This meter met International Organization for Standardization's criteria but not the American Diabetes Association's stringent criteria. The monitor produced precise readings throughout the concentration range and results correlated closely with the reference method. The measured total error was 6.39% (less than allowable total error of 10%). The method reached 6 sigma at glucose levels of 6.66 and 18.87 mmol/L and a sigma of 3 to 4 at glucose level of 2.49. Repeatability and intermediate precision were acceptable.**

Discussion: **We concluded that the overall performance of this instrument is reasonable but in hypoglycemic range, multiple control rules and control materials are required to assure the desired quality is achieved.**

Key words: Blood Glucose Self Monitoring, Diabetes Mellitus, Point of Care Systems

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Introduction

The prevalence of diabetes in Iran in 2008 is reported as 8% (1). Considering the high prevalence and in order to lessen the great burden of the disease, it is necessary to encourage diabetic patients to use SMBG devices to achieve optimal glycemic control (2, 3). Instruments invented for self-monitoring of blood glucose (SMBG) provide minimum procedures for blood collection and fully automated glucose assays which enable patients and nonlaboratory health care providers to monitor blood glucose levels (point of care testing, POCT). Regarding the reliability and validity of these instruments however, the evidence is not conclusive and their use is precluded for diagnosis of diabetes mellitus (4). In addition, the quality control rules to assure that these methods meet the required analytical or clinical quality are not specified. Local health care facilities should assess the performance of these devices before recommending them to patients in order to preclude adverse effects associated with low accuracy or precision of these devices. Unfortunately, no internationally accepted standard procedure for validation exists to date and the introduction of a wide variety of these devises causes problems regarding quality management of these methods. Statistical techniques for comparing monitor readings with reference observations and error grid analysis (5, 6) have been used to evaluate the quality of glucose monitoring systems.

The international organization for standardization (ISO) has recommended that total error of SMBG monitors be within ±0.83 mmol/L of the lab method for glucose concentrations <4.16 mmol/L and within ± 20% for glucose values ≥4.16 mmol/L (7). The American Diabetes Association (ADA) recommends meter readings be within 5% of the reference results (8).

"Operational process specifications have been derived from an analytical quality-planning model to assess the precision, accuracy, and quality control needed to satisfy Proficiency Testing (PT) criteria. These routine operating specifications are presented in the form of an OPSpecs chart, which describes the operational limits for imprecision and inaccuracy when a desired level of quality assurance is provided by a specific QC procedure" (9).

Based on CLIA, criteria for acceptable performance in proficiency testing, allowable total error for glucose (TE_a) is 10% and estimated sigma values 2.9 to 3.3. TE_a is comprised of imprecision and bias of a method. Six sigma quality management provides industries with a tangible estimate of method quality. Westgard J.O. applied the sigma scale to analytical processes (10). The higher the accuracy and precision of method, the higher the sigma metric and the easier the quality control of the method. Six sigma is the highest level of performance reached by best quality products. The recommended minimum acceptable process capability for health systems is 3 sigma (11).

In this study, we evaluated the performance of Accu-check Active glucometer (Roche Diagnostics, Mannheim, Germany) which is frequently used in clinical and outpatient care. For this, we used power function graphs, operational process specification charts and six sigma scale along with classical reliability and validity testing.

Materials and Methods

Consecutive non-selected type II diabetic patients from an outpatient clinic were recruited. Informed consent forms were signed by all the participants. The study was approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences. Exclusion criteria included hematocrit levels below 25% and above 55%. Unstable specimens, i.e. those with two reference measurement results not within 4% or 0.22 mmol/L, were also excluded (ISO).

We employed a split-sample design (12) that tests both the reference and monitor methods with a portion of the same test specimen. We used this scheme for glucose is unstable and chemical stabilizers interfere with test principle according to the user's manual. An expert technician performed the venipuncture from the brachial vein and collected the specimens in EDTA containing tubes. A portion of the blood sample was obtained for the first reference method test, then the duplicate monitor test was done, and finally a sample for the second reference method test was obtained. The samples obtained for the first and second reference tests were centrifuged within five minutes of the

duplicate monitor tests and tested within 60 minutes of the monitor tests (13). Some samples went under glycolyzation by 37° C water bath, in order to get adequate number of samples with desired low glucose concentration.

The monitor was operated by a trained technician according to the instructions of the manufacturer. The test was based on glucose dye oxidoreductase mediator (pyrroloquinoline quinone -dependent glucose dehydrogenase mediator reaction). The monitor calibration procedure programmed it for use with a specific lot number of reagent test strips and required a chip supplied with each lot of reagent test strips to be inserted into a port on the monitor. A control solution test was performed each time a new vial of strips was opened and regularly thereafter according to the user's manual provided by the manufacturer. The monitor's visual control system was also used to help detect dysfunction.

The reference measurements were done by Hitachi 704 biochemistry analyzer using Pars Azmoon enzymatic kit (Pars Azmoon corp., Tehran, Iran) which employs glucose oxidase method. The reference method was monitored for stability during the experiment using appropriate quality control materials and procedures. A hematocrit test was done for each sample. The whole blood equivalent of the reference method values were obtained by the following equation:

Plasma glucose equivalent= Whole blood × 1.12

The monitor results were compared with the average of the duplicate reference measurement results and the differences were calculated in mmol/L when the reference average result was <4.16 mmol/L or as a percentage when the reference average result was≥ 4.16 mmol/L. The accuracy of the glucometer was evaluated according to analytical goals proposed by ISO (total error within ±0.83 mmol/L of the lab method for glucose concentrations <4.16 mmol/L and within ± 20% for glucose values ≥4.16 mmol/L, 95% of the time) (7) and ADA (<5% deviation from the reference value) (8).

We used Bland and Altman's difference plot (14) to assess agreement between the glucometer and the reference method. This plot assesses the magnitude and dispersion of the difference between the methods, graphically. Briefly, the mean and SD of the differences between the monitor and reference values were calculated. The mean ± 1.96 SD represented the 95% confidence interval.

Slope, intercept, and correlation coefficient (R) were calculated from the method comparison between the monitor and reference method. The Passing and Boblock method was used to compare monitor readings to reference results. The regression equation was used to estimate the bias:

Bias = (slope × selected concentration of glucose [mg/dL]) + Y intercept

Sigma metrics were calculated from bias, CV and quality requirement (or TE_a specified by the CLIA PT criteria) (15) according to the following equation:

Sigma Metric = (TE_a – Bias) / analytical standard deviation of the method (10).

If the sigma metric is above 3, it is recommended to use a QC Design tool like the QC Validator software programs (16). In other words, the quantitative relationship between the sigma metric of a method and appropriate QC procedures can be determined by a critical-error graph superimposed by a sigma scale.

We evaluated the repeatability and intermediate precision according to the ISO 15197 protocol. Repeatability is defined as the "Precision under conditions where independent test results are obtained with the same method on identical test items in the same location by the same operator using the same equipment within a short interval of time." To determine repeatability, ten meters were used. Per each meter, ten test strips from the pertinent vials were assigned and dosed repeatedly with one of the venous blood samples. Five blood samples of different glucose levels were used. Intermediate precision is defined as the "Precision under conditions where test results are obtained with the same method on identical test items in the same location, but where other variables such as operators, equipment, calibration, environmental conditions, and/or time intervals differ." To determine intermediate precision, ten meters were used. The assigned test strips were dosed with one of the three levels of Accu-Check Active control

solutions repeatedly for ten days, so for each control solution, ten different determinations were made on ten meters (30 measurements per meter).

The statistical analyses were done by SPSS version 15 and QC Validator 2.0 software programs. Statistical significance was defined as $P<0.05$.

Results

During the period from June 2005 to September 2006, one hundred type II diabetic patients, aged 20 and above, from the outpatient clinic of the Shahid Labbafinejad Hospital (affiliated with Shahid Beheshti University of Medical Sciences, Tehran, Iran) were recruited. Most of the patients (65%) used insulin. The hematocrit of the patients ranged from 37% to 52% which was within the operative specifications of the meter. Blood glucose values ranged from 1.66 to 23.32 mmol/L to cover all the clinically relevant glucose ranges. An analysis of outliers was done and four specimens were excluded.

According to the Passing and Boblock regression analysis the intercept was equal to 1.0 with simultaneous 95% confidence interval of -0.2500 to 4.4125. The slope was 1.0 with the simultaneous confidence interval of 0.9750 to 1.0122.

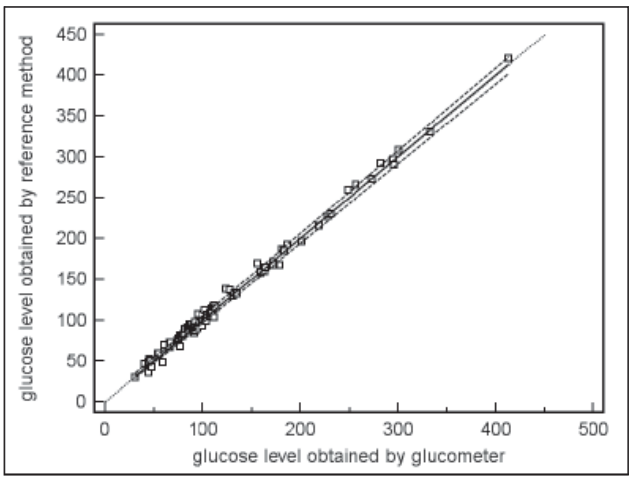

Fig. 1: Accu-Check Active monitor readings vs. reference method results (N= 94)

Bland and Altman graphic presentation is shown in Fig. 2. The mean global difference is close to zero, indicating the small mean difference between the methods.

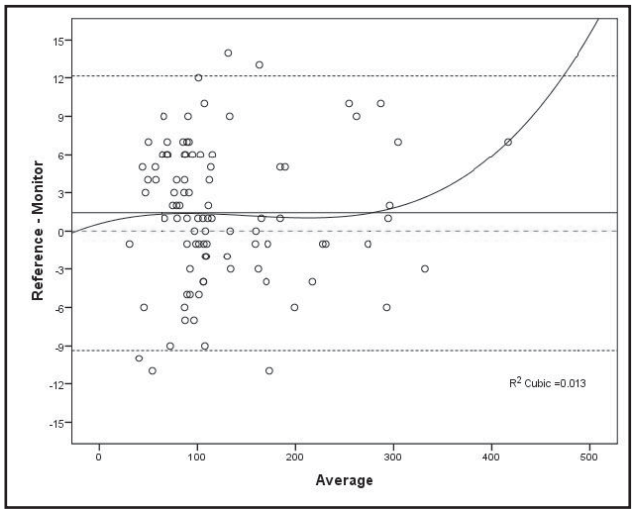

Fig. 2: Difference against mean for glucose concentration

The Accu-Chek Active Glucose Monitoring System met the ISO 15197 requirements for accuracy. All of the 94 samples were within the minimum acceptable performance criteria. The measured bias (1.11 mg %) is less than the allowable bias (<6 mg%, according to the CLIA). The measured total error is 6.39%, which is less than allowable total error (10%). This glucometer did not reach the ADA recommendation of 100% of readings within the 5% deviation limit. According to sigma scale, the method performed differently at different levels. We got a 6 sigma metric at glucose level of 6.66 and 18.87 mmol/L and a sigma metric of 3 to 4 at glucose level of 2.49 mmol/L. Figures 3 and 4 illustrate the OPSpecs charts for a 10% total error requirement (15). In these charts the top lines show the maximum allowable inaccuracy and imprecision when the procedure were perfectly stable and no QC was required. The lower lines represent the operational limits for a measurement procedure that is unstable and subject to systematic errors that should be detected by different QC procedures. To locate the operating point of the procedure the imprecision and inaccuracy of the procedure are plotted on the chart. The line above the operating point shows that the pertinent QC procedure will provide the stated level of quality assurance (9).

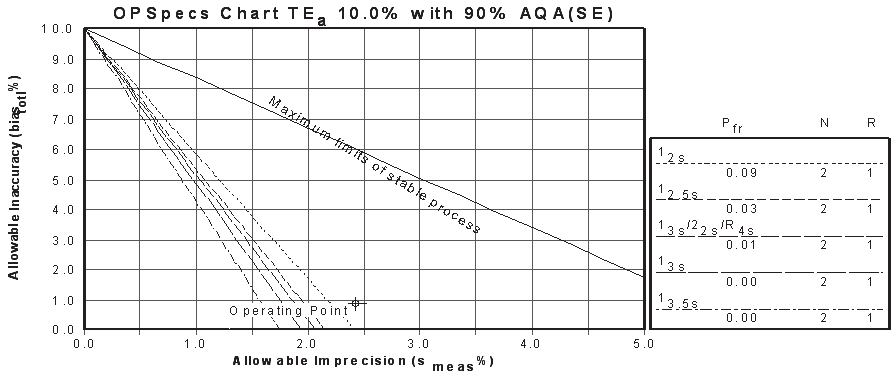

Fig. 3: Operational process specification chart with TEa of 10% at glucose level of 45 mg/dL

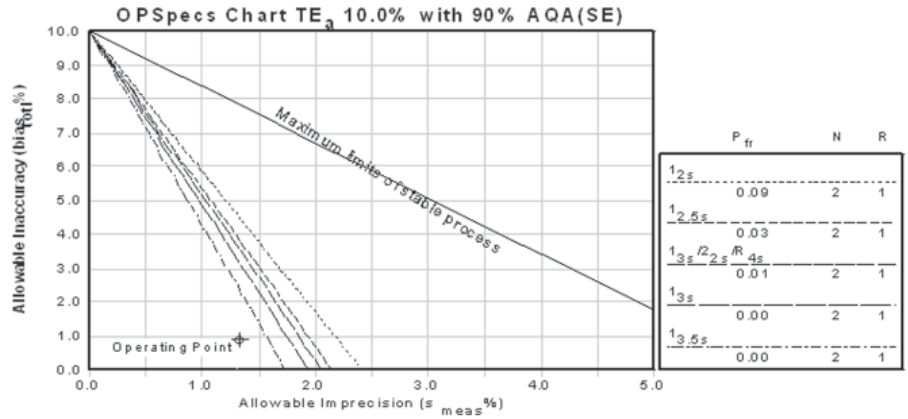

Fig. 4: Operational process specification chart with total error of 90% at glucose level of 120 mg/dL

The coefficient of variation of the reference method was <3% during the study period. The monitor yielded overall means and CVs for the low, normal, and high control solutions, respectively, 0f: 43.9, 3.4% (n=100), 119.9, 2.8% (n=100), and 337.8, 3.6% (n=100).Within and between run CVs (1.36 and 3.31%, respectively) were lower than the maximum allowable values (2.9 and 5.7%, respectively).

Discussion

According to the ISO 15197:2003 and CLSI criteria regarding the analytical performance of monitor systems, the meter performed acceptably in the study's testing condition. Based on the sigma scale approach, the operating point of the monitor system was satisfactory in normo- and hyperglycemic range. According to the results, this monitor system failed to meet the criteria proposed by ADA similar to most of other published studies.

This study shows that criteria proposed by different organizations give different answers regarding the acceptable performance of the methods while the charts of operational process specifications, instead of returning a yes / no answer, help the user to bring the quality of the method under control. In addition, some of the other methods, which have been applied in this type of studies including linear regression and Bland and Altman approaches, reveal some shortcomings that have previously been debated. Linear regression shows the degree of correlation between methods neglecting the numerical agreement (17). Bland and Altman method assumes an equal severity of errors for the whole blood glucose range and normal distribution of the errors, which may not be the case.

We showed that in lower glucose level, more sophisticated control rules should be applied to control the quality of the monitor process. This finding was in concert with that of Puntmann *et al.* (18) and Wehmeier *et al.* (19) who found that in the hypoglycemic range, glucometers under study were less reliable.

It is worth stating that our study focuses merely

on analytical performance, which represents only a percentage of the errors in the total testing process, which includes all pre-, intra-, and post analytical phases. Moreover, this study is based on a split specimen design that is insensitive to total testing process problems that can occur before specimens are collected and after results are obtained by the analytical process (12). As it has been stated that most of the errors of monitors involve the user and not the system itself, future studies should additionally consider other sources of error. In addition, the values of sigma metrics presented here are based on the performance of the method in hands of a trained technician. To obtain a more accurate specification of this method, further studies should be done with the instrument in hands of patients, which is expected to yield poorer results. Therefore, in addition to striving for improvements in analytical performance, appropriate training of the glucometer users should be addressed.

In our study, the subjects were recruited from an outpatient clinic, so the obtained performance characteristics should not be generalized to e.g. the critically ill patients (20) or neonates.

We used one factory new device in hands of a trained technician so the interdevice reliability, in-use assessment (effect of long-term use), and user acceptability were not addressed in this study (21). One other limitation of this study was that we did not consider the biologic and medication interference (22).

Conclusion

We concluded that Accu-check Active provided reliable measurements of blood glucose in terms of analytical performance and though it is likely to show more variation in performance in the hypoglycemic range, its overall performance could be appropriate for monitoring blood glucose values in patients with diabetes.

Acknowledgments

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