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SYMPOSIUM

Whole Blood Glucose Standard Is Key to Accurate Insulin Dosages

Bradford Hunsley, B.S. and Wayne Ryan, Ph.D.

Abstract

Introduction:

There is no available glucose standard for whole blood. None of the various glucose controls can be used as standards (calibrators) for glucose meters or test strips. This article describes the need for a whole blood glucose standard for areas such as manufacturing or proficiency evaluations. Furthermore, it describes the performance of the standard developed by Streck. Implementation of a whole blood glucose reference standard may allow the manufacturers of products for the diabetes health care industry to reduce the level of systematic difference between true blood glucose values and those obtained by point-of-care (POC) glucose meters.

Methods:

Glucose agreement data were collected across four prominent POC glucose meters representing >97% of all meters reporting data in the 2006 College of American Pathologists survey. Glucose concentrations of whole blood were adjusted to replicate the concentrations contained in the blood glucose standard developed by Streck. Commercial glucose controls, provided by the respective strip manufacturer, remained unaltered and were tested in accordance with the manufacturer's recommendations.

Results:

Only slight variations in hematocrit, surface tension, and viscosity were measured over a period of 90 days with the Streck Blood Glucose Standard compared to fresh whole blood at time zero. Glucose measurements on whole blood and the blood glucose standard were in agreement for all four commonly used glucose meters. In contrast, there is a lack of agreement between a manufacturer's set of recommended aqueous-based glucose controls in measurements taken on their POC meter relative to the YSI. Finally, the blood glucose standard demonstrated stability in 35-day open- and 110-day closed-vial assessments.

Conclusions:

Results of our experiments illustrate the ability of the blood glucose standard to closely mimic whole blood results. In addition, the blood glucose standard shows good open-vial and closed-vial stability at 6ºC.

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Author Affiliation: Streck, Omaha, Nebraska

Abbreviations: (ADA) American Diabetes Association, (POC) point of care, (SMBG) self-monitoring of blood glucose

Keywords: commutability, diabetes, glucose meters, glucose standard, glycemic control, glycolysis, insulin dosage, point of care

Corresponding Author: Bradford Hunsley, B.S., Streck, 7002 South 109 Street, Omaha, NE 68128; email address bhunsley@streck.com

Introduction

Inaccuracy Results in Insulin Dose Errors

The American Diabetes Association (ADA) has been urging point-of-care (POC) glucose meter manufacturers to reduce the level of deviation between "true" glucose measurements and those of home self-monitoring of blood glucose (SMBG) to less than 10% since 1987.[1] More recently, the ADA updated its recommendations to reduce glucose meter error to less than 5%.[2] Because insulin dosage is based on a patient's blood glucose level, inaccurate glucose values can result in improper treatment.

Standardization of glucose products for diabetic patients could improve accurate insulin dosages for diabetics. Boyd and Bruns[3] used a computer-generated model to simulate a series of blood glucose measurements with a wide range of error. They used a sliding scale for insulin dosage to evaluate treatment errors based on inaccurate glucose levels. When imprecision and bias errors were reduced to 10%, the model indicated that 16 to 45% of the insulin doses would still be inaccurate. For insulin dosages to be accurate more than 95% of the time, the combined imprecision and bias errors must be less than 1.5%.

POC Glucose Meter Study

Weitgasser and colleagues[4] carried out a study to examine the improvements of four new POC glucose meters compared to four older models. At that time, none of the meters evaluated could achieve the ADA-recommended guidelines. In fact, the meter with the most accurate patient blood glucose values achieved less than 5% error for only 57% of its measurements.

Methods

A Glucose Standard for Improving Meter Accuracy

A commutable glucose standard with the properties of whole blood may be the key that will allow meter and test strip manufacturers to achieve the recommendations of the ADA.

Streck is a leader in the area of cell stabilization and has employed both its technology and its expertise to assist the POC glucose industry by developing a whole blood glucose standard. The Streck Blood Glucose Standard is manufactured with stabilized whole blood and maintains stable glucose values for up to 110 days at refrigerated temperature (2–10ºC). More importantly, the product mimics the flow rate and performance of fresh whole blood on glucose test strips. Some of the characteristics of whole blood critical to the performance of the glucose test strip are hematocrit, viscosity, and surface tension. **Figure 1** compares these parameters in whole blood to the stabilized Streck product.

Figure 1

Parameter	Whole blood (K_3EDTA)	Streck Blood Glucose Standard		
	Baseline	Initial	Day 60	Day 90
Hematocrit[a] (%)	40.8	39.6	40.5	41.5
Viscosity (cP)	3.4	3.4	3.4	3.4
Surface tension (dynes/cm)	58.6	57	56.3	55.8

[a]*The hematocrit can be altered without changing the relation to fresh whole blood.*

Figure 1. Comparison of physical characteristics reported with fresh whole blood collected in K_3EDTA and the Streck Blood Glucose Standard.

Why Mimic Whole Blood?

Blood glucose test strips are designed to separate the red blood cells in whole blood from the plasma. The separation technologies consist of materials that filter the red blood cells from whole blood or cause red blood cell aggregation. The plasma portion of the blood is then able to carry the glucose to the analyzing region of the test strip, which reacts quantitatively with glucose. The glucose meter determines glucose levels via kinetic measurement. The viscosity and composition of whole blood, as well as the time required to remove the red cells, affect the flow rate and the time it takes for the plasma to reach the analytic portion of the test strip. Aqueous glucose solutions lack the cellular impedance and viscosity to obtain sample delivery time on the test strip that mimics whole blood. The glucose in an aqueous control reaches the analyzing system faster than in whole blood and adversely affects the kinetic rate of reaction. Because there are a number of variables like this that can alter glucose meter readings, a whole blood reference standard is needed to ensure the performance of the instruments and test strips.

Results

The Streck Blood Glucose Standard Satisfies Commutability Requirements and Replicates Whole Blood

The development of a reference standard from whole blood represents challenges in all instances where commutability is essential. A commutable reference material or standard will provide comparable results regardless of the analytical methods or instruments used to perform the testing.[5] Thus, the glucose standard must yield true and accurate values regardless of the glucose strip lot or the meter performing the measurement. An aqueous control product, designed for one instrument, is (1) not universally compatible with other glucose strips and meters and (2) not suitable for the preparation and calibration of test strips. Only a product that mimics whole blood, the intended substance for use on glucose test strips, with a stable glucose concentration will reduce the imprecision with current manufacturer calibration methodologies.

The Streck Blood Glucose Standard is the first available commutable calibration and verification material that provides stable glucose values on virtually all glucose meters and test strips. **Figure 2** illustrates values obtained for whole blood and the Streck Blood Glucose Standard on four meters representing >97% of all meters reporting data in the 2006 College of American Pathologists survey. The Streck Blood Glucose Standard reproduces values obtained with whole blood on all four glucose meter platforms. Thus, the product recovers the glucose concentrations of fresh whole blood, illustrating its compatibility with existing glucose products and its utility for manufacturers and proficiency providers.

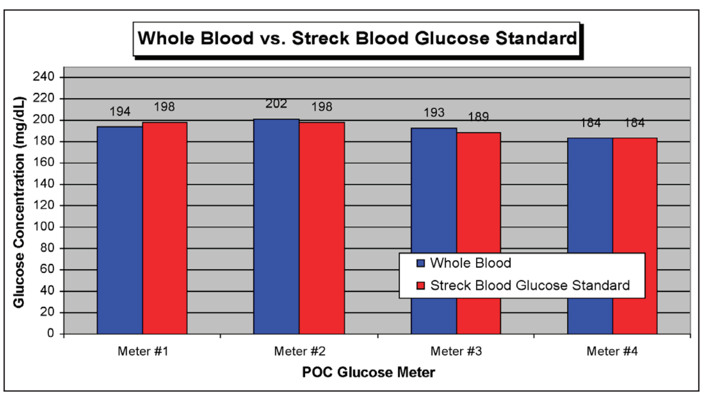


Figure 2. The Streck Blood Glucose Standard replicates glucose recoveries reported with glucose-adjusted fresh whole blood on four popular POC glucose meters. Data were collected from whole blood collected in K_3EDTA and the Streck Blood Glucose Standard with true glucose concentrations of 180 mg/dl. True glucose concentration was confirmed on the YSI analyzer. Data were collected in triplicate with three different reagent test strip lots (n = 9).

Aqueous Glucose Solutions Do Not Provide Desired Performance

In contrast, aqueous glucose control products produce values that are not representative of the true glucose concentration. The glucose control product supplied with the glucose meter provides results for that glucometer and the test strips assigned with it. The glucose values do not necessarily relate to the true glucose concentration and are not commutable; the control cannot be used on a different manufacturer's meter or strips. To illustrate, **Figure 3** shows the lack of agreement between true glucose values measured by the YSI analyzer and values obtained by a POC meter. The POC system overrecovers glucose levels, and the glucose concentrations reported do not accurately reflect the values obtained by the YSI instrument.

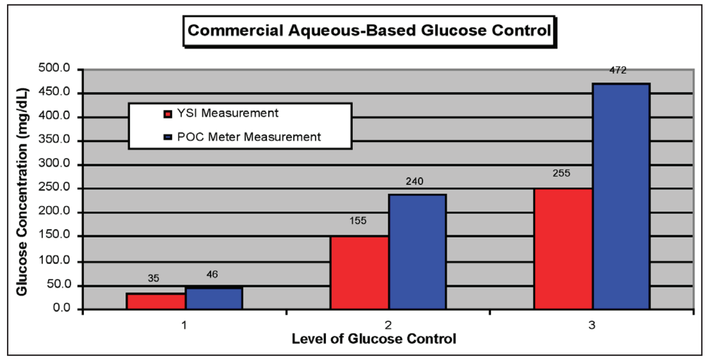


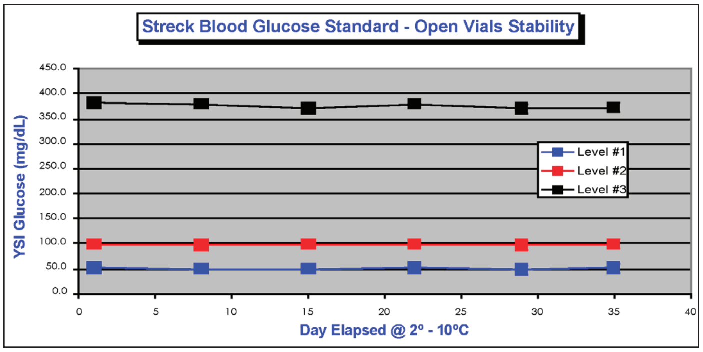
Figure 3. Glucose concentrations obtained from a commercially available aqueous-based glucose control on the YSI analyzer and the POC device. Comparison of mean glucose values recovered with a commercially available aqueous control solution on a typical POC glucose meter (blue). True glucose concentrations were measured on a YSI analyzer (red). These values were 35, 155, and 255 mg/dl. Data were collected in triplicate with three different reagent test strip lots (n = 9).

The Optimal Glucose Control Mimics Whole Blood but Remains Stable

To enhance its utility, the Streck Blood Glucose Standard maintains stable glucose concentrations for a significant amount of time. **Figure 4** shows 35-day open-vial stability (top) and 110-day closed-vial stability (bottom) of the Streck Blood Glucose Standard at refrigeration. The product is also stable for 14 days at ambient temperatures (data not shown). The extended stability characteristics of the Streck Blood Glucose Standard make it suitable for applications of the diabetes health care industry.

Fixation Techniques and Glycolysis Hindered Prior Attempts to Stabilize Whole Blood

Prior attempts to create a stable whole blood glucose control have been unsuccessful because of the inherent instability of whole blood and the difficult requirements described for mimicking its properties. Some have tried using red blood cell fixation, but this renders the red blood cell membranes rigid and impairs their ability to behave like fresh cells. Glucose test strips are designed to capture or aggregate normal, flexible blood cells. This difference has an effect on the flow rate of the sample and, ultimately, on the glucose concentration read by the meter.



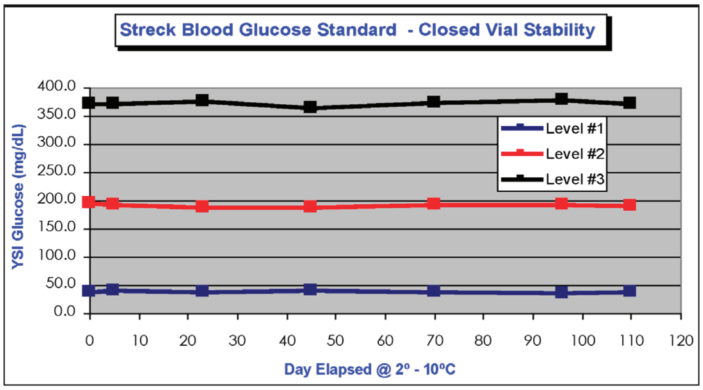


Figure 4. Stability characteristics reported with the Streck Blood Glucose Standard. Glucose stability data were collected on a YSI analyzer. Data illustrate 35-day open-vial stability (top) and 110-day closed-vial stability (bottom) at refrigeration temperatures.

Glycolysis creates another barrier for the development of a whole blood standard. The red blood cells in whole blood continue to metabolize plasma glucose at a rate of 5 to 7% per hour.[6] This is an issue for patient samples drawn in hospitals and physician offices where delays in sample analysis are common. To circumvent this, many clinical laboratories use blood collection tubes containing sodium fluoride to measure blood glucose levels in patients. Sodium fluoride, an antiglycolytic agent, inhibits the ability of the red blood cells to metabolize free blood glucose. However, sodium fluoride is a slow-acting preservative. Glucose levels decline for the first few hours after exposure to the inhibitor and are then maintained for a period of 72 hours.[7] The stability of blood preserved with sodium fluoride is not long enough to make it useful for a whole blood glucose control.

Clinical settings may employ centrifugation to separate plasma from red blood cells to reduce the effects of glycolysis on patient samples. A whole blood specimen should be centrifuged within 60 minutes of collection[7]; however, POC settings are unlikely to have a centrifuge on hand. Moreover, glucose levels in plasma do not remain stable when stored[8] because residual platelets and white blood cells continue to metabolize glucose in plasma samples.[9,10] These characteristics, along with the exclusion of cellular material, make plasma another poor choice as a potential control material.

Another compound that has been used to stabilize glucose levels in whole blood is glyceraldehydes.[11] L-Glyceraldehyde has been shown to inhibit glycolysis in whole blood for 8 hours, providing additional time for patient sample transport,[11] but it does not provide enough stability to be useful as a preservative for a diabetes glucose standard.

None of the aforementioned methods used to control glycolysis are suitable for use as a blood glucose standard with POC test strips, even for relatively short periods. Only the Streck Blood Glucose Standard provides the benefits of whole blood characteristics and performance with extended glucose stability.

Conclusions

Upon review of the POC glucose meter industry, it is clear that standardization of glucose products for diabetic patients should be considered a necessity. The current allowable glucose meter error is too great and should be reduced for patients to obtain optimal control of the disease. The ADA recognizes that the variability among glucometers may be due, in part, to matrix effects and the lack of an available glucose standard for manufacturers to assess the accuracy of blood glucose meters and test strips.

The Streck Blood Glucose Standard is the first commutable standard for the POC glucose meter industry to provide extended glucose stability in the form of whole blood. The Streck Blood Glucose Standard provides manufacturers of glucose products the opportunity to reduce error by incorporating a standard in place of existing protocols that require either whole blood, which lacks stability, or aqueous controls, which do not perform like whole blood. These improvements will help alleviate the existing complications with calibration and verification and allow POC glucose strip and meter manufacturers to achieve the high standards of accuracy and precision recommended by the ADA.

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