Between-Lot Variation in External Quality Assessment of Glucose: Clinical Importance and Effect on Participant Performance Evaluation

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Background: External quality assessment schemes (EQAS) are conducted to evaluate user performance (participant assessment) and to assess different methods and instruments (method assessment). The quality of control materials is crucial to achieving these goals. Inconsistencies in between-lot variations detected by use of different control and sample materials may affect EQAS outcomes.

Methods: For the Accu-Chek Sensor, Precision Xtra, Ascensia Elite, and HemoCue 201 glucometers, 3 different lots of glucose strips were used with each instrument. Method assessment results from analysis of capillary blood and 3 control materials were used to calculate between-lot differences. A simulation study was performed to evaluate the effect of between-lot variation on participant assessment results.

Results: With the Precision Xtra, the results obtained with EQA control material mirrored those obtained with capillary blood, but for the other instruments, we found between-lot differences of as much as 1.3 mmol/L, which were substantially greater than those found with capillary blood and of clinical importance at decision limits. The simulation study showed an effect on participant assessment results related to the target values, with the percentage of poor results decreasing (38%, 10%, and 4%) with the use of common, method-specific, and lot-specific target values, respectively.

Conclusions: Between-lot variation may influence participant EQA results for participant and method assessments. The clinical relevance of between-lot variation discovered in EQAS using noncommutable control materials should be examined by use of native blood samples.

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The goals of external quality assessment schemes (EQAS) are to evaluate user performance (participant assessment) and to assess different methods and instruments (method assessment) (1–3). The quality of the control materials used is crucial to achieving these goals. Ideally, control materials should behave similarly to human patient samples, and the target value of the control material should be determined by a reference method (4).

Glucometers used at physicians’ offices or for self-monitoring of blood glucose use either capillary or venous whole blood. Whole-blood glucose is not stable, and different additives have different effects on the various meters (5, 6). It therefore is difficult to use a single control material in EQAS for all glucose meters (7). Method-specific target values are commonly used (8). The Norwegian Quality Improvement of Primary Care Laboratories (NOKLUS) uses 2 different control materials in EQAS, depending on the type of meter. For each survey, NOKLUS registers the instrument as well as the lot number of glucose strips used by participating office laboratories. Our surveys have indicated that the results of glucose measurements are affected by the lot of the blood glucose testing strips used as well as the type of glucometer. These results raise 2 important questions. (a) Would between-lot variation detected by use of control materials also be observed in clinical situations in which fresh capillary blood is used? (b) Should participant assessment results be compared against a lot-specific target value rather than a method-specific target value, i.e., what effects does the use of different target values have on participant assessment results?

We present results obtained with different lots of glucose strips for 4 widely used meters, comparing capillary blood and 3 EQA control materials.
Materials and Methods

In the NOKLUS EQAS for glucose, control materials in 2 concentrations are sent to ~1900 participating Norwegian office laboratories twice a year. All participants return the results together with information about the instrument and lot number of strips used. More than 20 different types of glucometers are represented in the EQA scheme. The 4 instruments included in the present study were used by approximately one-third of the participants.

STUDY DESIGN

On the basis of routine EQAS carried out with Sugar Chex (Streck Laboratories) or stabilized EDTA blood (Sero AS) as control materials, 3 different lots of glucose strips were selected for each of the 4 glucometers: Accu-Chek Sensor (Roche Diagnostics), Precision Xtra (Abbott Laboratories/Medisense), Ascensia Elite (Bayer Diagnostics), and HemoCue 201 (HemoCue) instruments (see section below on instrument and lot selection). The 12 lots were investigated in the laboratory by use of capillary blood samples and stabilized EDTA blood. All but the lots from the HemoCue 201 were further examined by use of Sugar Chex and a control material used for Norwegian hospital laboratory EQAS, a liquid frozen serum pool (Sero AS). For each instrument, differences among the 3 lots were first calculated for capillary blood material and thereafter for each of the 3 control materials. In addition, results with capillary blood were compared with those from a conventional reference method. Finally, results from the NOKLUS October 2003 EQAS for glucose were used to simulate the effects of between-lot variation on participants assessments.

INSTRUMENT AND LOT SELECTION

This study included the instruments that were most widely used and that demonstrated significant between-lot variation in the NOKLUS October 2003 EQAS for glucose. Glucose strips from each of 3 lots were selected for each instrument according to the following criteria: (a) one lot number had significantly different results from the two others and (b) one lot number had results that were similar to the average of all lot numbers. As an example, results from the EQA survey for the Ascensia Elite are shown with all different lot numbers as well as the lots selected for our study (Fig. 1).

TEST MATERIALS

Capillary blood samples were obtained from 12 persons: 5 healthy volunteers and 7 patients with diabetes. The mean plasma glucose value was 7.53 mmol/L (range, 5.11–14.78 mmol/L) as measured by the Advia 1650 (with reagents from Bayer). The 12 capillary blood samples were measured once with each of the 3 different lots on each instrument (total 12 measurements on the 4 instruments). In addition, capillary blood samples for reference measurements (see below) were taken before and after meter measurements. The order of the lot numbers was altered between patients, and the procedure time did not exceed 10 min. The difference in glucose values between the first and the last sample as measured by the conventional reference method had to be <4% (9). Two series of measurements were excluded because of differences >4%.

The control materials used were Sugar Chex Proficiency [7.1 mmol/L; lot no. 32660723 (expiration date, January 19, 2004)]; stabilized EDTA blood (4.08 mmol/L EDTA, 1.8 mmol/L sodium iodoacetate) from 1 donor, adjusted with d-glucose to 7.38 mmol/L (measured on Advia 1650); and fresh-frozen human serum [7.04 mmol/L, as measured by use of an isotope-dilution gas chromatography–mass spectrometry reference method (4)]. For each control material, 10 measurements were carried out with each of the 3 different lots on each type of instrument. The order of the 3 lot numbers was altered between each measurement.

CONVENTIONAL REFERENCE METHOD

The conventional reference method for plasma glucose was performed on the Advia 1650 (Glucose Hexokinase method II; product no. B01-4597-01). The method was verified by the control solution [frozen human serum pool targeted with the isotope-dilution gas chromatography–mass spectrometry reference method for glucose (4)] used by NOKLUS in the EQAS for glucose for hospital laboratories. For instruments that reported whole-blood values, i.e., the Accu-Chek Sensor and HemoCue 201, results were multiplied by 1.11 (10) to be comparable to plasma values.

PARTICIPANT ASSESSMENT RESULTS

Participant assessment results in the EQAS for glucose were designated as good for results within the target interval (the method-specific target value ± 0.1 mmol/L) ± 5%; acceptable for results between ± 5% and ± 10% outside the target interval; and poor for results more
than ± 10% outside the target interval. The method-specific target value was calculated as the median of all results from participants using a particular instrument, after outliers had been excluded (11).

STATISTICS
We used an assumed CV of 5% and calculated that 10 replicate measurements (or 10 patients in case of capillary whole blood) would be required to detect a difference of ~8% between 2 lots (90% power using a 2-sided 0.05 level test). Between-lot variation and instrument bias were assessed by t-tests, and statistical significance was set to 5%. When selecting lots for inclusion in the study, we set statistical significance to 0.01 because of multiple comparisons.

A simulation study was performed because the number of participants using each lot number was rather small because of the large number of lots in use. The simulation was based on results from the NOKLUS October 2003 EQAS for glucose, including the 4 instruments and lots that were part of the present study. Using the mean (SD) for each of the 12 lots in 2 concentrations (~7 and ~20 mmol/L), we created 24 gaussian distributions, each comprising 100 values.

Results
EFFECT OF USE OF CAPILLARY BLOOD AND DIFFERENT QUALITY-CONTROL MATERIALS ON BETWEEN-LOT VARIABILITY
Between-lot variation was affected by the instrument, the lot of glucose strips, and the test material (Fig. 2). For the Precision Xtra, the capillary blood results mirrored those of the EQA control materials. For the Accu-Chek Sensor and Ascensia Elite, between-lot variations of up to 1.3 mmol/L were obtained with certain control materials and differed by as much as 0.8 mmol/L from between-lot variations obtained with capillary blood. For the HemoCue 201, there was a difference of <0.3 mmol/L between all 3 lots for EDTA blood but no difference when capillary blood was used.

BIAS
As shown in Fig. 3, results from the HemoCue 201 using capillary blood showed no deviation from the conven-
The present study showed between-lot variation in results for both capillary blood and control materials (Figs. 1 and 2). Between-lot differences were as much as 1.3 mmol/L with control materials. Such differences are clinically important at critical decision limits for glucose (9, 17). It is therefore important to undertake measures to determine whether the between-lot differences observed in EQAS are likely to occur when native blood is used. On the other hand, between-lot differences present in capillary blood will probably not always be reflected when control materials are used, and the absence of between-lot differences in EQAS is no guarantee that such differences do not occur when native blood samples are tested. Manufacturers should therefore be urged to produce more consistent glucose strips, and commutability studies should be carried out to ensure that control materials give valid results.

Because there is much variability among lots, the lot used by the most participants will influence the target values to a greater extent than the other lots, and participants with an aberrant lot will have a greater probability of obtaining a poor assessment result. If a lot-specific target value is used, these participants will have a much higher probability of obtaining a good result.

The simulation study showed that there is a large effect on participant assessment results whether a common target value for all methods, a method-specific target value, or a lot-specific target value is used. Therefore, lot-specific target values should be used for conducting participant assessments because the performance of the participants thus would not be adversely affected even if the method and lot used have poor quality. This approach will be difficult to implement, however, because there are many different lots of strips on the market at the same time and the number of participants using each of the lots is rather small. In our October 2003 EQAS for glucose, there were 1834 participants using 24 different instruments and ~400 different lots of strips. An alternative procedure for EQAS for glucose is to register lot numbers so that participants can be given a fair feedback report. For example, the feedback report may inform a participant assessed as poor that the lot used deviated significantly from the method target median.

Although evaluation of the trueness of meters and strips was not the main objective of this study, it is interesting to note that only the HemoCue results did not show any deviation from the results of the conventional reference method, a finding that is in agreement with some studies (18–20) but in contrast to others (21–23). For one of the instruments, the Accu-Chek Sensor, one lot showed a significantly larger deviation from the reference method than the other two lots. Between-lot variation is important in instrument evaluations, and more than one lot should always be included (24, 25).

In conclusion, clinically important between-lot variations detected by use of control materials may not be detected...
with capillary blood and vice versa. In addition, EQA organizers should register lot numbers of glucose strips so that information on lot variation can be included in feedback reports. The use of lot-specific target values, however, is not feasible.

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References