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Comparison of a human portable blood glucose meter, veterinary portable blood glucose meter, and automated chemistry analyzer for measurement of blood glucose concentrations in dogs

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Objective—To compare blood glucose concentrations measured with 2 portable blood glucose meters (PBGMs) validated for use in dogs (PBGM-D) and humans (PBGM-H) and an automated chemistry analyzer.

Design—Validation study.

Sample Population—92 samples of fresh whole blood and plasma from 83 dogs with various diseases.

Procedures—Each PBGM was used to measure whole blood glucose concentration, and the automated analyzer was used to measure plasma glucose concentration. Passing-Bablok linear regression and Bland-Altman plots were used to determine correlations and bias between the PBGMs and the automated analyzer. Calculated acceptability limits based on combined inherent instrument imprecision were used with Bland-Altman plots to determine agreement. Clinical relevance was assessed via error grid analysis.

Results—Although correlation between results of both PBGMs and the standard analyzer was > 0.90, disagreement was greater than could be explained by instrument imprecision alone. Mean difference between PBGM-H and chemistry-analyzer values was –15.8 mg/dL. Mean difference between PBGM-D and chemistry-analyzer values was 2.4 mg/dL. Linear regression analysis revealed proportional bias of PBGM-H (greater disagreement at higher glucose concentrations); no proportional bias was detected for PBGM-D. No constant bias was detected for either PBGM. Error grid analysis revealed all measurements from both PBGMs were within zones without an anticipated effect on clinical outcome.

Conclusions and Clinical Relevance—Neither PBGM had exact agreement with the automated analyzer; however, the disagreement detected did not have serious clinical consequences. Our findings stressed the importance of using the same device for monitoring trends in dogs and using instrument-specific reference ranges. (*J Am Vet Med Assoc* 2009;235:1309–1313)

Accurate and efficient assessment of an animal's blood glucose concentration aids clinical management of many pathological conditions that cause hyperglycemia or hypoglycemia, including diabetes mellitus. Most clinicians have access to laboratories with automated chemistry analyzers that quantify blood glucose concentration via a hexokinase or glucose oxidase reaction; however, the concentration can be measured several ways. Much less commonly, blood glucose concentration is quantified via photometric, oxidation-reduction, or measuring-electrode techniques.[1] Use of automated analyzers is the standard method for evaluating blood glucose concentration, but potential disadvantages include blood sample volume requirements and slow turnaround time.

Portable blood glucose meters are handheld instruments that use reagent test strips to provide immediate results. Most PBGMs are designed to use capillary blood by drawing the blood into the reaction chamber of the test strip by capillary action or having a drop of blood applied to the application zone of the test strip. The test strips contain a porous membrane that separates erythrocytes so that analysis is performed on the resultant plasma.[1] Because of the small sample volume required and the immediate results, PBGMs offer an important advantage relative to automated laboratory analyzers in the critical care setting. In addition, PBGMs allow home monitoring for better control of blood glucose concentration in subjects with diabetes mellitus.

To date, the veterinary literature only contains data from the evaluation of human PBGMs; however,

Abbreviations

CI	Confidence interval
CV	Coefficient of variation
PBGM	Portable blood glucose meter
PBGM-D	Portable blood glucose meter validated for use in dogs
PBGM-H	Portable blood glucose meter validated for use in humans

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in the past several years, several veterinary-specific PBGMs have entered the market.[2,3] Therefore, the purpose of the study reported here was to compare results of PBGMs validated for use in animals or humans with those of a standard laboratory analyzer. All glucose-measuring devices described in this report quantify and report a value for plasma glucose concentration. However, to maintain consistency among this report, clinical jargon, and other literature on this topic, the term blood glucose will be used in place of plasma glucose.

Materials and Methods

Dogs—This prospective study was conducted with 92 blood samples from 83 client-owned dogs with various signalments and diseases. The need for a serum biochemical analysis was the only inclusion criterion. No dog for which such an analysis was performed was excluded.

Experimental protocol—Blood samples were obtained from dogs in the order in which they were evaluated. Samples were collected from a jugular, cephalic, or lateral saphenous vein with a 20- or 22-gauge needle and a syringe, and a drop of fresh whole blood was immediately analyzed by use of each PBGM. The remaining whole blood was transferred into tubes containing lithium heparin[a] immediately after collection. Anticoagulated blood was centrifuged and plasma was harvested within 15 minutes after collection.

The PBGMs were consistently operated in similar environmental conditions by the principal investigator or by a technician, in accordance with the manufacturer's recommendations. Both PBGMs were calibrated per manufacturers' instructions at the initiation of the study and upon use of each new container of test strips. Calibration included use of control solution and check test strips. Plasma glucose concentration was measured with the automated analyzer by licensed medical technologists.

Analyzers—The automated chemistry analyzer[b] measures glucose concentration via an enzymatic hexokinase oxidase reaction, and results are detected spectrophotometrically. The analyzer requires 40 µL of plasma or serum for each test; the linear range is 2 to 750 mg/dL.[4] Results are generated in approximately 6.5 minutes.

The PBGM-H[c] makes use of a glucose dehydrogenase reaction and reflectance photometry to detect blood glucose concentration. Operation of the glucometer requires that 1 µL of whole blood be applied directly to the test strip. The manufacturer recommends use of capillary rather than venous blood. The linear range is 10 to 600 mg/dL, and results are obtained in as few as 5 seconds.[5]

The PBGM-D[d] is validated for use in dogs and cats. It makes use of a glucose oxidase reaction and electrochemical biosensor technology. Operation of the glucometer requires that 1 µL of whole blood be pulled into the chamber via capillary action. The manufacturer states that the PBGM-D is validated for both capillary and venous blood. The linear range is 10 to 600 mg/dL, and results are obtained in a mean of 9 seconds.[6]

Data analysis—Data were analyzed by use of commercial medical statistics software.[e] The automated analyzer was used as a reference standard to which the PBGMs (index tests) were compared. Glucose values reported as high or low by the PBGMs were excluded for the purposes of the statistical analysis because only numerical values could be compared with results from the automated analyzer. Method comparison was conducted as described elsewhere.[7]

Briefly, descriptive statistics were generated for each instrument. Bland-Altman difference plots were constructed for results of each PBGM, compared with results of the automated analyzer. Correlation coefficients (r) were calculated, and values were interpreted as follows: 0.90 to 1.00, very high correlation; 0.70 to 0.89, high correlation; 0.50 to 0.69, moderate correlation; 0.30 to 0.49, low correlation; and 0 to 0.29, little, if any, correlation.[8] Precision data (CVs) for each instrument were obtained from the manufacturers of the instruments. For each PBGM, the combined inherent imprecision of the PBGM and the automated analyzer was calculated by use of the following equation[7]:

$$CV_{\text{Both Methods}} = (CV^2_{\text{Method 1}} + CV^2_{\text{Method 2}})^{0.5}$$

For each datum point, acceptance limits[7] for the difference between instruments were calculated as follows:

$$\text{Acceptance limits} = 0 \pm (1.96 \times CV_{\text{Both Methods}} \times \text{mean}_{\text{Both Methods}})$$

If > 5% of the differences between PBGM and automated analyzer were outside of the calculated acceptance limits, the null hypothesis that the 2 methods are identical was rejected.

Passing-Bablok linear regression analysis was used to detect constant and proportional bias. If the 95% CI for the slope did not include the value of 1, this was considered evidence of proportional bias. If the 95% CI for the y intercept did not include the value of 0, this was considered evidence of constant bias. Overall performance of each PBGM, as compared with that of the automated analyzer, was evaluated on the basis of correlation, mean difference, and presence or absence of constant or proportional bias.

In addition, PBGM data were assessed for clinical relevance by use of error grid analysis, which focuses on the clinical relevance of error.[9,10] The error grid divided the plot of chemistry-analyzer values (x-axis) versus the PBGM values (y-axis) into 5 zones associated with the following 5 risk levels: zone A, no effect on clinical action; zone B, altered clinical action but no or minimal effect on clinical outcome; zone C, altered clinical action with a likely effect on clinical outcome; zone D, altered clinical action with considerable medical risk; and zone E, altered clinical action with dangerous consequences. This specific error grid was developed by physicians, assuming a target blood glucose concentration between 70 and 180 mg/dL, with blood glucose values < 70 or > 240 mg/dL requiring intervention.[9,10] One hundred endocrinologists were given datum points of measured blood glucose values versus true blood glucose values for hypothetical patients and asked to classify the disagreement between values into 1 of the 5 risk zones. The endocrinologists' responses were averaged to create the error grid.

Results

Blood samples from 63 dogs were evaluated for glucose concentration with both PBGMs in addition to the automated analyzer. Samples from an additional 29 dogs were evaluated with only the PBGM-D and the automated analyzer.

Blood glucose concentrations measured with the PBGM-H ranged from 51 to 414 mg/dL, in addition to 1 H (high value) reading that corresponded to an automated-analyzer value of 685 mg/dL. Blood glucose concentrations measured with the PBGM-D ranged from 52 to 488 mg/dL, in addition to 1 H reading that corresponded to an automated analyzer value of 685 mg/dL. The correlation was very high between both PBGMs and the automated analyzer (PBGM-H, $r = 0.99$; PBGM-D, $r = 0.93$). Bland-Altman plot analysis revealed a mean difference of −15.8 mg/dL between the PBGM-H and the automated analyzer (**Figure 1**) and a mean difference of 2.4 mg/dL between the PBGM-D and the automated analyzer (**Figure 2**). For both PBGMs, many values (70% for the PBGM-H and 47% for the PBGM-D) were outside of calculated acceptability limits based on the combined inherent imprecision of the glucometer and automated analyzer. On the basis of these findings, results of neither PBGM was considered identical to those of the automated analyzer.

Passing-Bablok linear regression analysis of PBGM-H values versus automated analyzer values yielded a y-intercept of 2.65 (95% CI, −5.64 to 9.94) and slope of 0.88 (95% CI, 0.83 to 0.95). On the basis of these findings, proportional, but not constant, bias was considered to exist. Linear regression analysis of PBGM-D values versus automated analyzer values yielded a y-intercept of −11.14 (95% CI, −41.00 to 3.14) and slope of 1.09 (95% CI, 0.96 to 1.40). On the basis of these findings, neither constant nor proportional bias was considered to exist. Therefore, the only statistically apparent bias was that the PBGM-H had proportional bias, yielding lower values than the automated analyzer at higher glucose concentrations.

Error grid analysis revealed that all measurements for both PBGMs were within zone A (no effect on clinical action) or zone B (altered clinical action but no or minimal effect on clinical outcome; **Figure 3**).

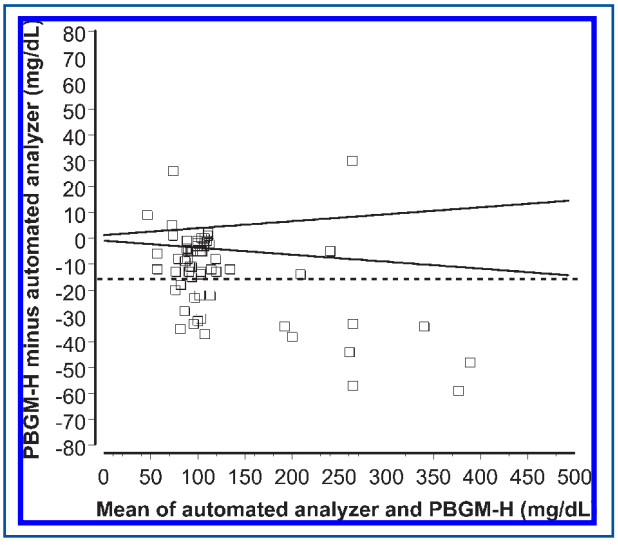

Figure 1—Bland-Altman difference plot of glucose concentrations measured with a PBGM-H and an automated chemistry analyzer in 63 samples of fresh whole blood and plasma from dogs with various diseases. Solid lines represent 0 ± (1.96 X $CV_{Both\ Methods}$ X $mean_{Both\ Methods}$). The space between the solid lines represents the limits within which the difference between the 2 methods must fall for the 2 methods to be considered identical. The dotted line represents the mean difference between the 2 methods, with results of the PBGM-H averaging 15.8 mg/dL lower than results of the automated analyzer.

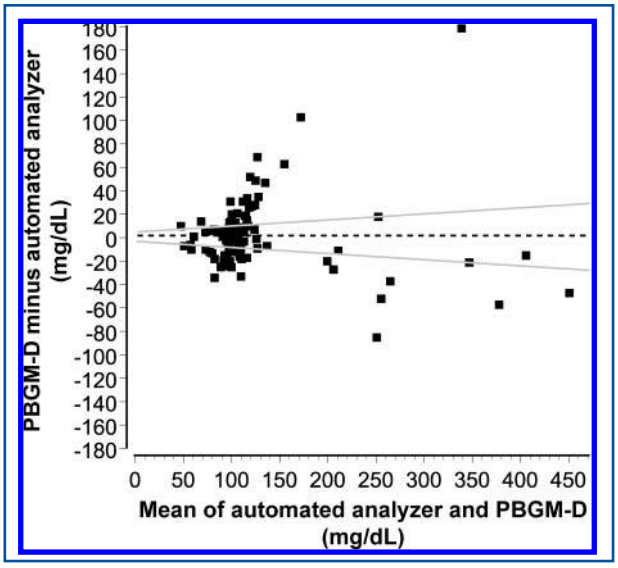

Figure 2—A Bland-Altman difference plot of glucose concentrations measured with a PBGM-D and an automated chemistry analyzer in 92 samples of fresh whole blood and plasma from dogs with various diseases. The dotted line represents the mean difference between the 2 methods, with results of the PBGM-D averaging 2.4 mg/dL higher than results of the automated analyzer. *See* Figure 1 for remainder of key.

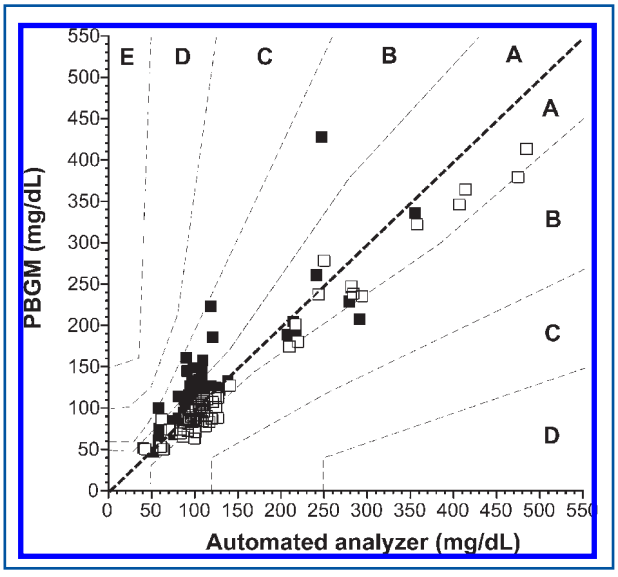

Figure 3—Results of error grid analysis for detection of type 1 diabetes by use of blood glucose concentration values from 2 PBGMs (PBGM-H, black squares; PBGM-D, white squares) and an automated chemistry analyzer as measured in 63 samples of fresh whole blood and plasma from dogs with various diseases. Zones A to E represent different consequences of an inaccurate glucose measurement: zone A, no effect on clinical action; zone B, altered clinical action without effect on clinical outcome; zone C, altered clinical action with an effect on clinical outcome; zone D, altered clinical action with possible considerable medical risk; and zone E, altered clinical action with possible dangerous consequences.

Discussion

Portable blood glucose meters are rapidly supplanting benchtop chemistry analyzers for immediate determination of blood glucose concentrations in critical care and home environments. New and different PBGMs are constantly becoming available, making it challenging to choose an appropriate meter, and very few of these PBGMs are designed and validated specifically for use in animals.

The first goal of the study reported here was to determine correlations between results of an automated analyzer and those of PBGMs. Correlation is a measure of association, rather than of agreement, between values.[7] In this context, association refers to the fact that 2 variables extend in the same direction, whereas perfect agreement refers to the fact that 2 methods yield the same numerical result. We found very high correlations between measurements of blood glucose concentration made by both PBGMs and the automated analyzer.

Our second goal was to assess agreement between results of the automated analyzer and the PBGMs (ie, how closely the values matched). Disagreement between 2 methods may be attributable to random error (imprecision) or systematic error (bias); bias can be classified as constant or proportional.[7] Constant bias refers to results of one method that are consistently higher or lower than results of another method (eg, one method always yields results 20 mg/dL lower than the other). Proportional bias refers to a difference that is dependent on the concentration or activity of the analyte in question.[7] Every routinely used laboratory method (so-called field method) has a certain amount of inherent random error (imprecision) attributable to testing conditions that can vary with such factors as operator and reagent used. In the present study, imprecision data were obtained from the instrument manufacturers, and the combined imprecision of the methods compared was used to determine whether differences in values obtained could be accounted for solely on the basis of inherent random error. Given these acceptability limits, we found that disagreement between both PBGMs and the automated analyzer could not be explained by inherent random error alone. For the PBGM-H, disagreement could be explained partially by proportional bias with more deviation at high blood glucose concentrations. We cannot exclude the possibility of proportional bias for the PBGM-D or of constant bias for either PBGM. The failure to detect any such bias may have been attributable to insufficient statistical power of the study caused by not enough samples.

Our third and most important goal was to evaluate the clinical usefulness of PBGMs, which was addressed by use of error grid analysis. Clinical relevance of PBGM measurements was historically assessed by evaluating the percentage of PBGM values within 10% of the reference value, as recommended by the American Diabetes Association.[11] The clinical consequence of a 10% deviation between the reference and measured values, however, varies on the basis of the absolute blood glucose values. The error grid was developed to eliminate this innate variation with the percentage deviation method.[9,10] Despite statistical evidence of disagreement between both PBGMs and the automated analyzer, our results indicated that the performance of both PBGMs is clinically acceptable. All datum points were in grid zone A or B, indicating no effect on clinical outcome. We used a human error grid, which, in our judgment, is generally well suited to application in dogs; however, use of a species-specific error grid may have yielded different results.

Clinicians use the reported results of instrument validation, performance statistics, method comparison, and other methods when choosing equipment for their clinics and when providing clients with advice on the purchase of equipment for home use. The prevailing opinion in human medicine is that clinical assessment that makes use of methods such as the error grid may be better than statistical models when comparing methods.[12,13] It is our opinion that both statistical evaluation and clinical assessment have value, particularly when used together. It is important for veterinary practitioners to understand that any statistical evidence of disagreement between methods must be interpreted in light of clinical relevance, bearing in mind such factors as intended application of an instrument or clinical decision-making thresholds.

Results of the present study indicated that neither PBGM had exact agreement with the automated analyzer. The PBGM-D values were slightly higher than those of the automated analyzer, whereas PBGM-H values were slightly lower. Although statistical evidence of proportional bias was not evident for the PBGM-D, both PBGMs had less agreement at high versus low blood glucose values. Because error grid analysis revealed this lack of agreement would not alter clinical outcome, the differences were considered not clinically relevant. This finding suggested that, although some bias exists, both PBGMs can be used effectively clinically. It also emphasized the benefit of consistently using 1 instrument when monitoring trends in an animal, as well as the importance of using instrument-specific reference intervals.

In our study, venous rather than capillary blood samples were used. Because of tissue utilization of glucose, postprandial capillary blood glucose concentrations are typically 20% to 25% (20 to 70 mg/dL) higher than those of concurrently obtained venous samples.[1] When food is withheld, the difference is much less, with capillary blood glucose concentration averaging only 2 to 5 mg/dL higher than that of concurrently obtained venous blood.[1] Dogs in our study were not uniform with respect to food withholding or feeding prior to sample collection, so it is impossible to predict the discrepancy between results for capillary and venous blood. However, all samples evaluated on all instruments were of venous origin, so all methods should have been affected similarly. We cannot be certain that repeating the study with capillary blood samples would yield identical results.

A limitation is that we did not obtain an Hct value for all dogs at the time of blood glucose analysis. Anemia and polycythemia falsely increase or decrease, respectively, PBGM measurements.[14] Hematocrit data were only available for a small subset of dogs, and values ranged from 25.9% to 59.2% (reference limits, 41% to 60%). Because Hct values were not available for all

dogs, the proportion of anemic or polycythemic dogs in the study was unknown and conclusions cannot be made about the affect of anemia and polycythemia on PBGM performance. All datum points were within zone A or B on the error grid, and so the potential effect of Hct on PBGM values was unlikely to be of clinical importance. Similarly, we did not separately analyze blood samples with evidence of hemolysis or lipemia. Depending on the method used to measure blood glucose, blood hemoglobin and bilirubin concentrations and lipemia can have various effects on assay results.[1] The PBGMs in our study make use of different methods of measuring blood glucose concentration and consequently have different innate inaccuracies.

Another limitation of our study was the low number of hypoglycemic blood samples (6 samples < 70 mg/dL as measured by the automated analyzer). We considered the possibility of creating artifactual hypoglycemia by diluting some samples with physiologic saline or delaying separation of plasma, but both methods were considered impractical because both PBGMs are validated by use of whole blood.

The present study revealed that the PBGM-H and PBGM-D are clinically acceptable methods of measuring blood glucose concentration in dogs. Both require a minute volume of blood and yield results within seconds. With the PBGM-H, the drop of blood must be applied to the test strip, but with the PBGM-D, the blood drop is drawn into the test strip via capillary action. Capillary action is preferable and more practical because it allows use of a lancet versus a needle and syringe. The advantages of a lancet include less restraint, pain, and stress for the animal, easier sampling of capillary versus venous blood, and improved owner success with home blood glucose monitoring.[15–17]

a. Vacutainer, Becton Dickinson, Franklin Lakes, NJ.
b. Hitachi 911, Roche Diagnostics, Indianapolis, Ind.
c. ACCU-CHEK Active, Roche Diagnostics, Indianapolis, Ind.
d. GlucoPet, Animal Diabetes, Janesville, Wis.
e. Medcalc, version 8.2.1.0, MedCalc Software, Mariakerke, Belgium. Available at: medcalc.be. Accessed Sep 15, 2009.

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