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Technical note: Evaluation of the diagnostic accuracy of 2 point-of-care β-hydroxybutyrate devices in stored bovine plasma at room temperature and at 37°C

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ABSTRACT

The use of point-of-care (POC) devices to measure blood metabolites, such as β-hydroxybutyrate (BHB), on farm have become an important diagnostic and screening tool in the modern dairy industry. The POC devices allow for immediate decision making and are often more economical than the use of laboratory-based methods; however, precision and accuracy may be lower when measurements are performed in an uncontrolled environment. Ideally, the advantages of the POC devices and the standardized laboratory environment could be combined when measuring samples that do not require an immediate result—for example, in research applications or when immediate intervention is not the goal. The objective of this study was to compare the capability of 2 POC devices (TaiDoc, Pharmadoc, Lübeck, Germany; Precision Xtra, Abbott Diabetes Care, Abingdon, UK) to measure BHB concentrations either at room temperature (RT; 20–22°C) or at 37°C compared with the gold standard test in stored plasma samples. Whole blood from multiparous Holstein dairy cows (n = 113) was sampled from the coccygeal vessels between 28 d before expected calving and 42 DIM. Whole-blood BHB concentrations were determined cow-side using the TaiDoc POC device. Plasma was separated within 1 h of collection and stored until analysis. A subset of stored plasma samples (n = 100) consisting of 1 sample per animal was chosen retrospectively based on the BHB concentrations in whole blood within the range of 0.2 to 4.0 mmol/L. The samples were analyzed for BHB plasma concentration using an automated chemistry analyzer (Hitachi 917, Hitachi, Tokyo, Japan), which was considered the gold standard. On the same day, the samples were also measured with the 2 POC devices, with samples either at RT or heated up to 37°C. Our study showed high Spearman correlation coefficients (>0.99) using either device and with samples at both temperatures compared with the gold standard. Passing–Bablok regression revealed a very strong correlation (>0.99), indicating good agreement between both POC devices and the gold standard method. For hyperketonemia detection, defined as BHB concentration ≥1.2 mmol/L, the sensitivity for both POC devices at RT and 37°C was equally high at 100%. Specificity was lowest (67.4%) for the TaiDoc used with plasma at RT and was highest (86.5%) when plasma was measured at 37°C with the Precision Xtra meter. Bland–Altman plots revealed a mean bias of 0.25 and 0.4 mmol/L for the Precision Xtra meter and TaiDoc, respectively, when tested on plasma at 37°C. Our data showed that both POC devices are suitable for measuring BHB concentration in stored bovine plasma, and accuracy was highest when samples were heated to 37°C compared with RT.
Key words: β-hydroxybutyrate, point of care, hyperketonemia, plasma

Technical Note

Subclinical hyperketonemia (**HYK**) in dairy cows has been defined as a BHB concentration in blood of ≥1.2 mmol/L (Oetzel, 2004; McArt et al., 2011). The gold standard spectrophotometric test for the determination of BHB concentrations in either plasma or serum is performed under controlled laboratory and environmental conditions. Each test costs $13 (as of December 2017) at the New York Animal Health Diagnostic Center (**AHDC**; Ithaca NY). Consequently, a lower-cost method with accuracy and precision comparable to the gold standard is preferable for routine measurement of BHB plasma concentration in the dairy industry. Several point-of-care (**POC**) devices were previously validated as cow-side methods to measure BHB concentration in bovine whole blood (Iwersen et al., 2009; Bach et al., 2016). Because of their user-friendliness and low maintenance and calibration requirements,

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POC devices are valuable tools in the field. Moreover, such a method may allow retrospective sample analysis under controlled environmental conditions (e.g., in research applications; Pineda and Cardoso, 2015) or when immediate results are not needed. Often, plasma is the sample of choice for storage, but available POC devices are calibrated and designed for use on whole blood, requiring validation of the use of this sample type in such applications. The Precision Xtra (Abbott Diabetes Care, Abingdon, UK) has been widely used as a diagnostic tool for HYK in the field (McArt et al., 2011; Mann et al., 2015) and was recently validated as a feasible method for estimating BHB concentration in bovine plasma and serum (Pineda and Cardoso, 2015). The approximate cost for each BHB test using the Precision Xtra was $1.70 to $4.00 (LeBlanc, 2010) plus the cost of the meter. Currently, the Precision Xtra test strips are available and sold only for human use in the United States, thus increasing the cost and reducing access for veterinary applications.

Recently, the TaiDoc POC device (Pharmadoc, Lübeck, Germany) was shown to measure BHB concentration in bovine whole blood with good accuracy and precision when testing was performed at room temperature (**RT**; Bach et al., 2016). The current cost for each TaiDoc strip is approximately $1.10, which makes this a convenient and cost-effective method for BHB testing. However, the temperature range for the TaiDoc meter is 5 to 40°C, similar to the Precision Xtra (10–50°C). Using POC devices on farm under conditions that differ from manufacturer specifications may lead to unknown variation in accuracy and precision due to limitations in temperature, humidity, and sample quality. A possible solution is to combine the ease and cost-effectiveness of POC devices with analysis in a controlled environment after sample collection. Plasma samples are easily obtained and BHB concentrations are stable in this sample type (Stokol and Nydam, 2005).

The objective of this study was to compare the results of the TaiDoc POC device for BHB concentrations in plasma either at RT or at 37°C with the results obtained with the gold standard method and a second POC device previously described for use in plasma samples (Precision Xtra; Pineda and Cardoso, 2015). Room temperature and 37°C were selected because laboratory tests are often carried out at either of the 2 temperatures. The 37°C temperature was selected to closely reproduce the conditions when using fresh blood samples on POC devices as well as to approximate the gold standard methodology.

All procedures for this experiment were approved by the Cornell University Institutional Animal Care and Use Committee (protocol no. 2014-0118 and 2015-0097). Holstein dairy cows (n = 113) from the Cornell University Ruminant Center (Harford, NY) were enrolled between January 2016 and July 2016. All cows were entering second or greater lactation and were sampled from 28 d before expected calving date until 42 DIM. Whole blood was collected 3 times per week from the coccygeal vessels using 10-mL blood collection tubes (Becton Dickinson, Franklin Lakes, NJ) containing 158 USP of sodium heparin and 20-gauge × 2.54-cm blood collection needles. Concentration of BHB was measured immediately after sample collection in whole blood using the TaiDoc POC device (Bach et al., 2016). After measurements were completed, blood samples were placed on ice and plasma was separated within 1 h of sample collection at 3,000 × *g* for 20 min at 4°C and stored in aliquots at −20°C until analysis.

A subset of plasma samples (n = 100) was chosen retrospectively based on the BHB concentrations in whole blood obtained with the TaiDoc POC device. Samples were included in this study based on whole blood BHB concentrations in increments of 0.1 mmol/L ranging from 0.2 to 4.0 mmol/L, with no more than 4 samples per increment. The plasma sample subset did not include more than 1 sample per animal to ensure independence of observations for statistical analysis. Samples were allowed to thaw on ice and were submitted to the AHDC for measurement of BHB concentration using a commercially available test kit (D-3 Hydroxybutyrate Ranbut, Randox Laboratories, Antrim, UK) on an automated chemistry analyzer at 37 ± 0.2°C (Hitachi 917, Hitachi, Tokyo, Japan) as the gold standard. The BHB plasma concentrations were measured on the same day as the gold standard and on the same aliquot with both POC devices as submitted to the AHDC. Meters were used at all times at RT (20–22°C). Plasma samples were measured first at RT with both devices and then at 37°C after heating plasma samples for at least 5 min in a water bath.

Data analysis was performed in SAS 9.4 (SAS Institute Inc., Cary, NC). Correlation coefficients (Spearman) between BHB gold standard and BHB concentrations obtained with both POC devices and samples at either RT or 37°C were computed using PROC CORR (SAS 9.4). Coefficient of variation (**CV**; %) was determined for 1 sample each in the low (0.8 mmol/L) and high (3.9 mmol/L) range of our data based on the gold standard method. For each sample, 12 measurements were performed with each POC device and with the sample at either RT or 37°C. Sensitivity of each method was calculated as the proportion of animals properly diagnosed as positive for HKY (BHB plasma concentration ≥1.2 mmol/L) among all animals identified as positive by each POC device compared with those clas-