J. Dairy Sci. 99:1–7
http://dx.doi.org/10.3168/jds.2016-11077

Technical note: Comparison of 4 electronic handheld meters for diagnosing hyperketonemia in dairy cows

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ABSTRACT

The objective of this study was to evaluate 4 handheld ketone meters for use in on-farm β-hydroxybutyrate (BHB) monitoring of hyperketonemia in transition dairy cows. Blood samples taken from 250 Holstein cows between 262 d pregnant and 15 d in milk were evaluated on 4 different handheld ketone meters: Precision Xtra (Abbott Laboratories, Abbott Park, IL), TaiDoc (Pharmadoc, Lüdersdorf, Germany), Nova Max (Nova Biomedical, Billerica, MA), and Nova Vet (Nova Biomedical). Samples were screened using the Precision Xtra and tested on the remaining 3 m if the sample BHB concentration fell into predetermined ranges. A total of 89 samples were used for analysis. Performance of each meter was compared with the average of 2 plasma BHB concentrations both determined by a gold standard spectrophotometric Randox assay performed at 2 independent laboratories. Agreement between the 2 laboratories was very strong (Pearson correlation = 0.998). All meters had Pearson correlation coefficients greater than 0.95. The Precision Xtra and TaiDoc meters were 100.0% sensitive and 73.5% specific at a BHB concentration cut point of 1.2 mmol/L. The Nova Vet and Nova Max meters had sensitivities of 94.9 and 74.4% and specificities of 91.8 and 100.0%, respectively, at the same cut point. Agreement between the gold standard and the handheld meter was the best for the Nova Vet meter when evaluated using a Bland Altman graph with a mean BHB difference of 0.08 mmol/L. Trends in bias were noted with the Precision Xtra and Nova Max meters resulting in increasing average discrepancy between the gold standard and the meter for both at higher plasma BHB concentrations and mean BHB differences of −0.34 and 0.26 mmol/L, respectively. The coefficient of variation was <10% for the Precision Xtra, TaiDoc, and Nova Vet meters, and <15% for the Nova Max meter. We conclude that the TaiDoc and Nova Vet meters, similar to the already validated Precision Xtra meter, are acceptable for use in on-farm testing for monitoring and treatment of hyperketonemia.

Key words: dairy cow, hyperketonemia, β-hydroxybutyrate, cowside meter

Technical Note

Most dairy cows undergo a period of negative energy balance (**NEB**) as they transition from late gestation to early lactation, a result of both an increase in energy requirements due to milk production and a decrease in DMI (Bauman and Currie, 1980; Baird, 1982; Herdt, 2000). In response to NEB, cows begin to break down fat stores; this increase in lipolysis releases fatty acids, which, among other avenues, leads to production of ketone bodies (Palmquist et al., 1969; Herdt, 2000). Thus, elevated concentrations of blood fatty acids and ketone bodies (e.g., BHB) are part of a normal adaptation of dairy cows to NEB in early lactation. However, excessive blood concentrations of fatty acids or BHB indicate a poor adaptation to NEB, which leads to an increased risk of detrimental health and production outcomes (Ospina et al., 2010; Chapinal et al., 2012; McArt et al., 2013). In addition, elevated levels of fatty acids and BHB can be detrimental to immune function (Hammon et al., 2006; Contreras et al., 2010; Ster et al., 2012). The incidence of elevated blood BHB ≥1.2 mmol/L in herds, or hyperketonemia (**HYK**), averages 40 to 60% in early lactation, and is thus a widespread issue in the dairy industry (Duffield et al., 1998; McArt et al., 2012).

Due to the high incidence of HYK, on-farm testing is important for monitoring and treatment of this disease. Recently, most on-farm testing has been performed using the Precision Xtra meter (Abbott Laboratories, Abbott Park, IL), a handheld blood ketone meter originally developed for human use. This meter has been well validated against the gold standard (spectrophotometric determination) for bovine BHB concentration in blood and found to be much more sensitive and specific

Received February 23, 2016.
Accepted July 14, 2016.
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than previous handheld urine and milk tests at diagnosing HYK (Oetzel, 2004; Carrier et al., 2004; Iwersen et al., 2009).

Over the past few years, additional BHB meters have been developed both for human and veterinary use, including the TaiDoc meter (Pharmadoc, Lüdersdorf, Germany) and the Nova Max and Nova Vet meters (Nova Biomedical, Billerica, MA). These meters have not yet been rigorously evaluated for their accuracy. The objective of this study was to determine the diagnostic performance of these additional handheld meters for cowside use to provide the dairy industry with additional options for on-farm HYK diagnosis and monitoring.

We conducted 2 experiments using the Precision Xtra, TaiDoc, Nova Max, and Nova Vet meters. Experiment 1 was designed to determine each meter's linearity compared with the gold standard method across a wide range of blood BHB concentrations. Experiment 2 was designed to determine each meter's repeatability. Heparinized blood samples were collected from 4 dairy farms in New York State from October until December 2015. Whole blood was collected from 250 Holstein cows between 262 d pregnant and 15 DIM using 10-mL heparinized vacutainer tubes and 20-gauge, 2.54-cm blood collection needles. Cows were sampled weekly during the dry period and daily following calving resulting in approximately 1,400 samples. Blood samples remained at room temperature until testing for HYK using a Precision Xtra meter, which occurred within 4 h of collection. As previous reports have shown no difference between BHB concentrations determined with handheld meters in fresh whole blood and samples stored at room temperature or with various additives, all samples were treated as though they were fresh, whole blood (Gordon et al., 2013; Iwersen et al., 2013; Megahed et al., 2015). Prior to testing, each blood sample was inverted gently 5 times; samples were evaluated following manufacturer guidelines.

For experiment 1, the first 5 blood samples with BHB concentrations (determined using a Precision Xtra meter) at or within previously chosen concentrations or concentration ranges were enrolled for a goal of 100 total blood samples. β-Hydroxybutyrate concentrations $\leq$0.5 mmol/L were measured as one range, concentrations from 0.6 through 1.5 mmol/L were evaluated in 0.1 mmol/L increments, concentrations from 1.6 through 2.5 mmol/L were evaluated in 0.2 mmol/L increments, concentrations from 2.6 through 4.0 mmol/L were evaluated in 0.5 mmol/L increments, and concentrations >4.0 mmol/L were measured as one range. No more than 5 samples in each BHB concentration or concentration range were enrolled; however, some BHB concentrations or concentration ranges had fewer than 5 enrolled samples. The following concentrations or concentration ranges contained less than 5 samples: 1.5 mmol/L (n = 3), 2.2 to 2.3 mmol/L (n = 4), 2.4 to 2.5 mmol/L (n = 1), 2.6 to 3.0 mmol/L (n = 4), 3.1 to 3.5 mmol/L (n = 4), and 3.6 to 4.0 mmol/L (n = 2). A total of 89 samples from 64 Holstein cows between 274 d pregnant and 14 DIM had BHB concentrations at the desired concentration or concentration range and were used in the analysis for experiment 1. Some cows contributed more than one sample to the study. These samples were immediately tested further using the TaiDoc, Nova Max, and Nova Vet meters. Prior to analysis by all meters, samples were again inverted gently and evaluated following manufacturers' guidelines and recommendations. The Nova Vet meter was used with the manual's recommended 1.25 calibration slope factor for testing bovine blood ketone concentrations. For experiment 2, 3 blood samples matching Precision Xtra BHB concentrations of 0.6 mmol/L, 1.4 mmol/L, and 3.2 mmol/L were further evaluated by the Precision Xtra, TaiDoc, Nova Max, and Nova Vet meters 10 times to analyze meter repeatability.

Following analysis, blood samples were centrifuged (10 min, 10,000 × g, 20°C) and plasma was stored in 2 aliquots at −80°C. After completion of meter testing, samples were submitted to the New York State Animal Health Diagnostic Center (**AHDC**; Ithaca, NY) and Imcarmed Lab (Saalfeld, Germany) for BHB concentration determination using gold standard spectrophotometric Randox assays (Randox Laboratories Ltd., Crumlin Co., Antrim, UK). For the 2 laboratories, intra-assay variation was less than 1% at both high and low control levels and the inter-assay variation was less than 5% at both control levels. Agreement between the AHDC and Imcarmed laboratories was determined using simple linear regression with JMP Pro (SAS Institute Inc., Cary, NC). Plasma BHB concentrations determined by the AHDC and Imcarmed laboratories had a very strong linear relationship (Pearson correlation = 0.998, slope = 1.03, $P < 0.001$). The gold standard for our analysis was calculated as the average BHB concentration between the AHDC and Imcarmed laboratories.

Linearity for each of the meters was determined using simple linear regression with JMP Pro, and test agreement between the gold standard and the handheld meter was determined via Bland Altman plots created by MedCalc (MedCalc Software, Ostend, Belgium). For repeated measurements, coefficients of variation were calculated for each meter in addition to the average variation from the mean. The sensitivity and specificity for each meter were determined at 1.2 and 3.0 mmol/L.

A total of 89 samples fit our criteria. One sample was excluded from analysis by all meters due to plasma