Evaluation of an Electrochemical Sensor for Measuring Blood Ketones

HILARY A. BYRNE, MRCP
KENNETH L. TIESZEN, PHD
SALLY HOLLIS, MSC

TIM L. DORNAN, FRCP
JOHN P. NEW, MRCP

OBJECTIVE — To evaluate the performance of a hand-held ketone sensor that is able to measure blood β-hydroxybutyrate (β-HBA) concentrations within 30 s in patients with diabetic ketoacidosis (DKA) and patients who attend a weight management clinic.

RESEARCH DESIGN AND METHODS — Two groups of patients were studied: 19 patients admitted with DKA and 156 patients attending a weight management clinic. Paired capillary and venous whole blood samples were measured using the ketone sensor and also using an enzymatic laboratory reference method.

RESULTS — The ketone sensor accurately measured β-HBA concentrations in patients with DKA (limits of agreement −0.9 to +1.0 mmol/l) or starvation-induced ketonemia (limits of agreement −0.5 to +0.5 mmol/l).

CONCLUSIONS — This ketone sensor accurately measures whole blood β-HBA concentrations within 30 s.

D iabetic ketoacidosis (DKA) is a serious complication of diabetes that is associated with considerable mortality and morbidity. Although the mortality rate diminished from 44% in the 1930s (1) to 16% in the 1970s (2) and to 3–5% in the 1980s (3,4), little improvement in these rates has been evident in recent years, and the incidence of DKA remains >20% in patients >65 years of age (5). Delays in the diagnosis and treatment of DKA are associated with an increase in morbidity and mortality (6). The diagnosis of DKA is not always easy. Between 1 and 8% of patients are ketoacidotic without significant hyperglycemia (6,7). Ketostix (Bayer Diagnostics, Stoke Poges, Slough, U.K.) measure urinary acetoacetate but not β-hydroxybutyrate (β-HBA), which is the predominant ketone body in DKA, and Ketostix may give false-negative results even if blood is tested. Laboratory measurement of β-HBA is not routinely available and takes too long to be of practical use in the emergency diagnosis and management of DKA. A combined glucose and ketone sensor that produces an electrical current proportional to blood β-HBA concentration has been developed (MediSense/Abbott Laboratories, Abingdon, U.K.) (Fig. 1). By using a 10-μl capillary blood sample, this hand-held sensor produces β-HBA results within 30 s. The aim of this study was to compare the accuracy and precision of the ketone sensor against an established laboratory enzymatic reference method (Procedure No. 310-UV 1994; Sigma Diagnostics, St. Louis, MO).

RESEARCH DESIGN AND METHODS — Two groups of patients who were suspected of having abnormalities of ketone metabolism were studied: patients with suspected DKA (group D) and patients treated with a very-low-calorie diet who attend a weight management clinic (group W). All subjects gave their informed consent, and the local ethics committee approved the study.

For group D, 500-μl capillary blood or 2-ml venous whole blood samples were collected during routine management. For group W, a single 500-μl capillary blood sample was obtained during the clinic visit. Sensor measurements were made in duplicate within 20 min for capillary samples and at the earliest opportunity (always within 12 h) for venous samples. Venous samples were refrigerated at 4°C before testing. One researcher (K.L.T.) performed all measurements. An electrochemical strip was inserted into the sensor to which 10 μl of whole blood were applied (Fig. 1). The β-HBA, in the presence of hydroxybutyrate dehydrogenase, was oxidized to acetoacetate with the concomitant reduction of NAD^+ to NADH. The NADH was reoxidized to NAD^+ by a redox mediator, and the current generated was directly proportional to the β-HBA concentration. After 30 s, the β-HBA concentrations (mmol/l) were displayed.

Hemoglobin was measured using a HemoCue AB analyzer (Angelholm, Sweden); room temperature and humidity were recorded using a Vaisala meter (Vaisala, Suffolk, U.K.). After initial testing with the ketone sensor, the samples were centrifuged, and the plasma was stored at −20°C pending analysis with an enzymatic laboratory method (Cobas Fara; Roche Diagnostics, Welwyn Garden City, U.K.).

To evaluate the precision of the ketone sensor, three venous whole blood samples with β-HBA concentrations of <1, 1.1–3.0, and 3.1–6.0 mmol/l as determined by the laboratory method were tested 20 times each within a 30-min period. Accuracy was assessed by comparing the sensor result with the reference method.

Statistical evaluation was performed using SPSS for Windows (SPSS, Chicago). To compare the two methods, the difference between the first sensor reading and the reference measurement was calculated for each sample and was analyzed using the method of Bland and Altman (8). Results are expressed as mean differences (limits of agreement). The effects of hematocrit, temperature, and humidity were examined using linear regression analysis between the difference between the mean sensor and reference results for each sample adjusted for type of patient (group D or group W) and the type of sample (venous or capillary). The reproducibility of the sensor was calculated as the within-sample SD of the two sensor measurements for each sample.

The precision of the sensor was calculated as the within-sample SD of 20 sensor measurements on three samples with low, medium, and high β-HBA concentrations.

RESULTS — A total of 224 β-HBA measurements from 19 patients in group D and 156 patients in group W were analyzed (β-HBA range 0.0–10.24 mmol/l). The sensor is programmed to give a "high" reading for β-HBA concentrations of >6 mmol/l as measured by the reference method. A total 13 samples were included from five patients in group D, and those samples gave high sensor readings. In 11 of the 13 samples, the sensor read "high" both times (means ± SD 7.5 ± 1.9 mmol/l [range 4.57–10.24]). One sample with a reference value of 4.87 mmol/l gave readings of high and 5.80 mmol/l; one sample with a reference value of 4.24 mmol/l gave sensor readings of high and 5.70 mmol/l. These high samples were excluded from further analysis. The agreement between the sensor and the reference method is shown in Table 1 and Fig. 3.

Humidity, temperature, and hematocrit had no effect on the reference measurements ($P > 0.38$) or on the difference
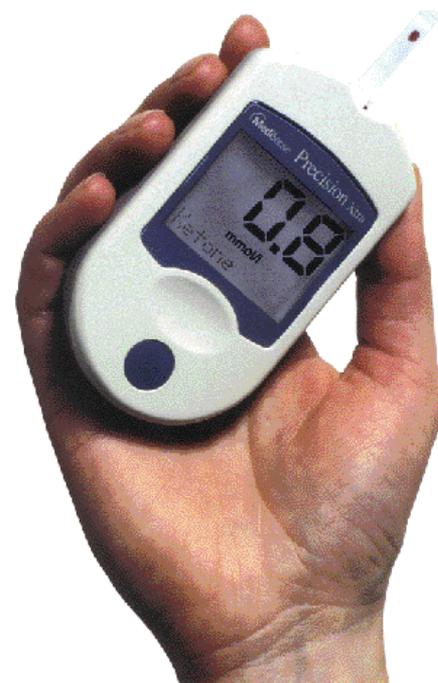

Figure 1—The combined ketone and glucose sensor.

Table 1—Concordance of β-HBA results obtained with the sensor and reference methods

|	Subjects/samples (n)	Reference values (mmol/l)	Sensor values (mmol/l)	Mean difference between sensor and reference (mmol/l)	Reproducibility SD (mmol/l)
All	175/211	1.23 ± 1.1	1.25 ± 1.2	+0.02 (−0.6 to +0.6)	0.13
Weight management (capillary)	156/156	1.05 ± 0.9	1.07 ± 0.9	+0.01 (−0.5 to +0.5)	0.12
DKA (all)	19/55	1.73 ± 1.4	1.78 ± 1.6	+0.05 (−0.9 to +1.0)	0.16
DKA (venous)	19/36	1.98 ± 1.6	2.07 ± 1.8	+0.09 (−1.0 to +1.2)	0.18
DKA (capillary)	7/19	1.25 ± 1.0	1.23 ± 1.1	−0.03 (−0.5 to +0.4)	0.13

Data are n, means ± SD, or differences (limits of agreement).
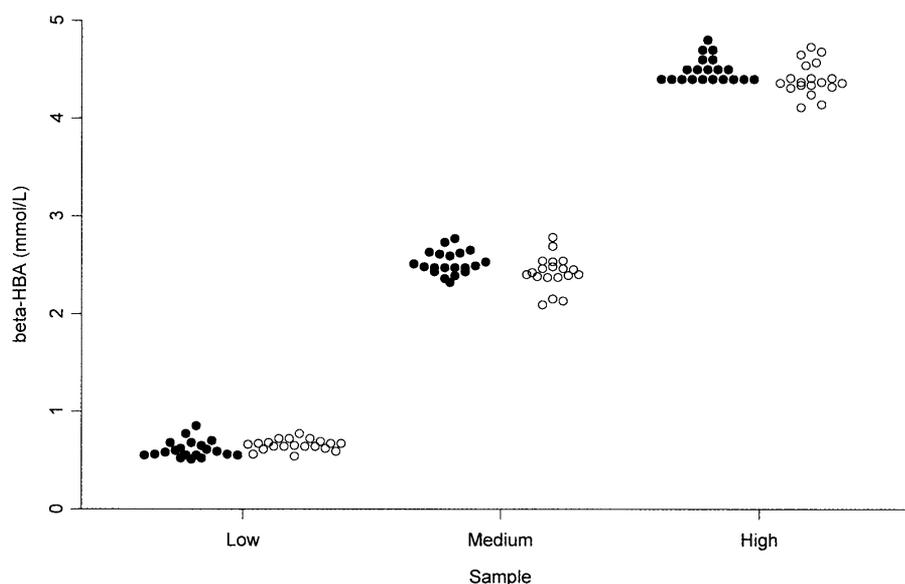
Figure 2—Scatterplot demonstrating the precision of the ketone measurements at high, medium, and low concentrations of β-HBA. ○, Reference; ●, sensor.
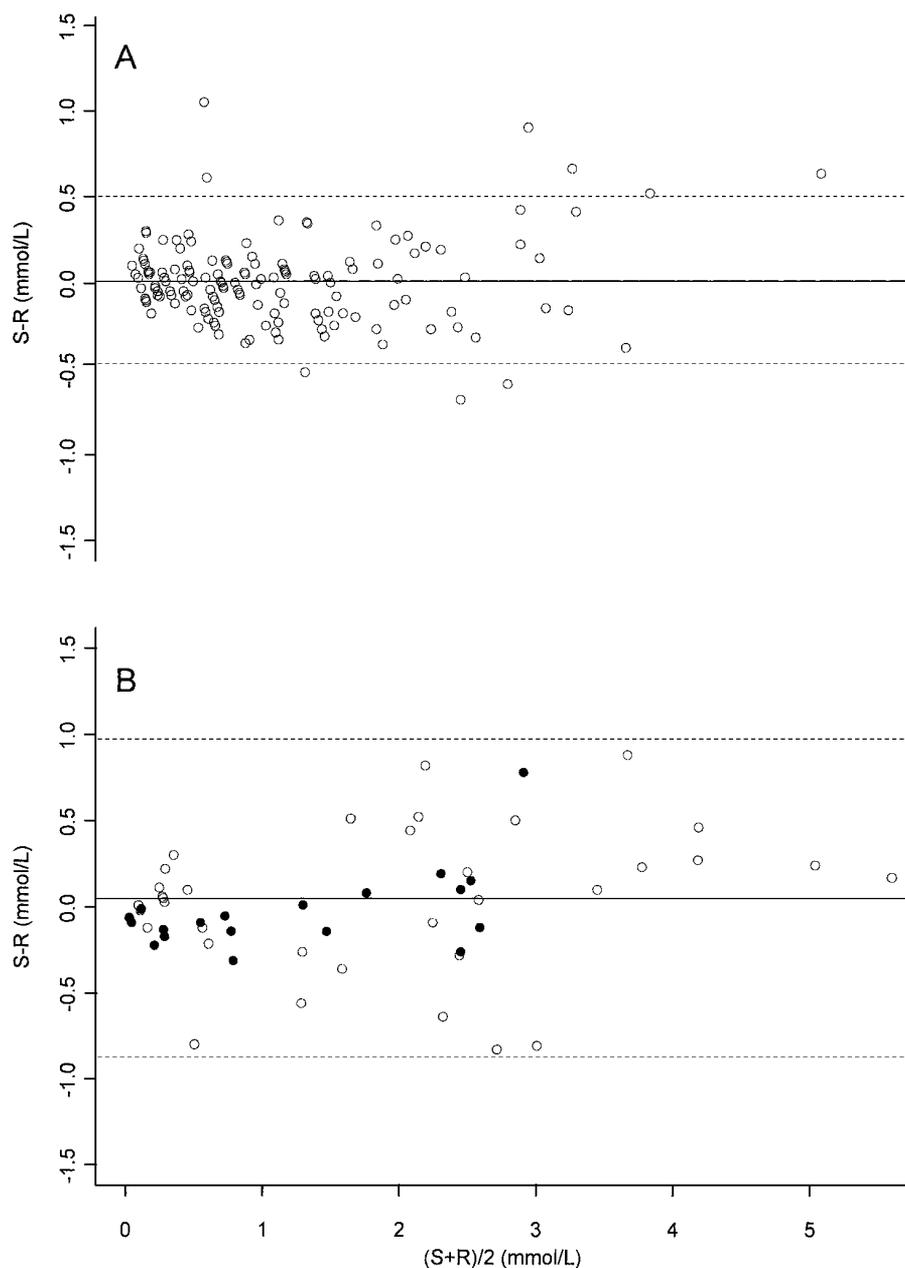
Figure 3—Bland and Altman (8) plot for β-HBA concentrations in capillary blood samples from patients attending the weight management clinic (A) and in patients with DKA (B) (○, capillary blood samples; ●, venous blood samples). The solid lines represent the mean difference, and the dotted lines represent the limits of agreement (means ± 2 SD). R, reference; S, sensor.

between the reference and sensor measurements (P > 0.18). The precision of the sensor and reference methods for high, medium, and low β-HBA concentrations is illustrated in Table 2 and Fig. 2.

CONCLUSIONS — This study demonstrates that this hand-held ketone sensor accurately measures whole blood β-HBA concentrations within 30 s. Previous ketone meters have required dilution of samples before testing, have measured over a restricted range (β-HBA <2 mmol/l), or have required prior measurement of acetoacetone concentrations, and these factors have limited their clinical effectiveness (9–11). In this study, the sensor gave results comparable with the reference method over a wide range of levels and gave accurate results up to 6 mmol/l. The precision, as measured by the coefficient of variation (CV), was very similar for both sensor and reference methods. The sensor tended to overestimate blood β-HBA concentrations slightly; however, high readings were only recorded when β-HBA levels were grossly elevated, and therefore patients would be correctly diagnosed as ketotic. Accuracy was similar with capillary or venous blood samples. Furthermore, the measurement of β-HBA by the sensor is not significantly affected by either acetone or acetoacetate, both of which may be increased in DKA (J. Bugler, MediSense/Abbott Laboratories, personal communication).

Its ease of use, small sample volume, short test time (30 s), automatic timing, and digital display make the ketone sensor a simple method for assessing β-HBA. The sensor is suitable for the early detection of ketosis and therefore DKA by both patients and health care professionals. This ketone sensor could complement real-time glucose measurements in the management of DKA.

Table 2—Precision of sensor and reference methods for three whole blood samples each measured 20 times

Sensor measurement (mmol/l)		Reference measurement (mmol/l)	
Means ± SD (mmol/l)	CV (%)	Means ± SD (mmol/l)	CV (%)
0.61 ± 0.09	14.6	0.66 ± 0.06	8.5
2.52 ± 0.12	4.7	2.42 ± 0.17	7.1
4.49 ± 0.12	2.7	4.40 ± 0.16	3.7

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