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Multicentric evaluation of eight glucose and four ketone blood meters

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ABSTRACT

Objectives: High precision meters for blood glycemia are mandatory for monitoring glucose status in patients, avoiding both hypo- and hyper-glycemia. Health care providers routinely used in both out- and in-patients point-of-care measurements of glucose and ketone. These measurements, frequently used for medical decisions, are known to be less accurate than those performed in laboratories.
Our aim was to evaluate, within the frame of an Assistance Publique-Hôpitaux de Paris (AP-HP) multicentric study, the performances of eight glucose and four ketone meters, either connected or non-connected to a laboratory software.

Design and methods: Glucose meter accuracy, precision, correlation with plasma glucose determined in central laboratories and hematocrit interferences were determined according to the ISO 15197:2003 norm. The same norm was applied for the determination of accuracy, precision and recovery of ketone meters for B-hydroxybutyrate measurements.

Results and conclusion: Among those meters, seven were considered as acceptable for glucose measurement and two for ketone measurement. Since all meters do not fit clinically relevant criteria, meters' performances have to be evaluated before use in clinical practice.

1. Introduction

The precise measurement of glycemia is mandatory for monitoring glucose status in patients, mainly to prevent both hypoglycemia and hyperglycemia, which can lead to severe injuries or even patient death. Venous plasma glucose measurements performed in central laboratories are recommended because of their accuracy and remain the reference method for the evaluation of glucose disorders, especially in diabetic patients. Nevertheless, the preanalytical phase has to be carefully monitored to avoid any significant errors, mainly linked to sample glycolysis and prevented by the use of acidic anticoagulant and/or glycolysis inhibitors. However, due to their accessibility, small volume of blood requirement, and quickness of analysis, glucose meters are frequently used as a surrogate for venous glucose assay. Thus, the performances of glucose meters have to be sufficient to be used in therapeutic decision-making, specifically with patients in intensive care units (ICU). As previously reported, a 5% analytical error in glucose measurement in diabetic patients leads to insulin dosage errors for 8 to 23% of patients, whereas it can reach 45% with an analytical error of 10% [1]. In the USA, according to the Food and Drug Administration (FDA), inaccurate glucose measurements have led to more than 12,000 serious injuries between 2004 and 2008 [2]. Two recent reports [3,4] of novel computer simulation studies of glycemic control in ICU patients provide advice regarding the performance requirements for glucose meters. Despite differences in outcome measures monitored (based on rates of hypo- hyper-glycemia, time in range, and glycemic variability [3], or based on probabilities of an error occurring in each error category [4]), results of both studies suggested that glucose meters with a mean absolute relative difference score <11% gave the best results and lowest frequencies of hypoglycemia [3,4].

The physicians must be aware of interferences occurring in glucose assay, mainly related to substances or patients' factors (including hematocrit and bilirubin, noticeably) [5]. The choice criteria for the meters have also to consider the enzyme used for glucose measurement, because

Abbreviations: POC, point-of-care; B-OHB, β-hydroxybutyrate; ISO, International Organization for Standardization; EGA, Error Grid Analysis; ADA, American diabetes association; NA, not available; Lev, level; LS, laboratory software; SD, standard deviation; CV, coefficient of variation; QC, quality control; Min, minimal.

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it was demonstrated that the glucose oxidase system could not be used in patients with artificial ventilation, whereas the use of the pyrroloquinoline quinone glucose dehydrogenase system was associated with interferences of different sugars used in perfusion solutions (including maltose, xylose, and icoextrin used in peritoneal dialysis) [5].

The accurate measurement of ketone blood level is also useful for monitoring at-risk diabetic patients. Ketone bodies refer to three different compounds: acetoacetate, β-hydroxybutyrate (B-OHB) and acetone, and their assays are mandatory to diagnose and manage potentially life-threatening ketoacidosis, particularly in children. Indeed, urine ketone detection is not sufficient enough since it may lead to either false positive results or, more importantly, to false negative results due to the inability of nitroprusside to react with B-OHB. Blood quantitative ketone assays performed in central laboratories are cumbersome and difficult to use, especially in a stat context. Currently used ketone meters detect only B-OHB, which seem efficient enough to predict ketoacidosis.

In clinical practice, comparisons of different glucose and ketone blood monitoring systems, either connected to central software or not, and independent of the manufacturers, are scarce. However, this type of evaluation is of critical importance, since a same patient may be treated on the basis of results from various devices including even home measurements. If the results obtained using different devices vary a lot, the management of patients could be deeply impacted. It is also crucial that the results obtained with different devices could be used independently of their origin, and most importantly lead to the same clinical answer.

Moreover, the criteria that are used for those evaluations may be different among studies.

In 1987, the Error Grid Analysis (EGA) was the first developed method to quantify the clinical accuracy of patient-determined blood glucose values [6]. EGA categorizes the relationship between a patient-generated blood glucose level and a reference blood glucose level in terms of the clinical status that would result from a treatment decision based on the patient-generated results.

Subsequently, Parkes and colleagues developed the consensus error grid (CEG) [7], a similar method for describing the accuracy of glucose meters based on clinical decision-making.

In 1987, the American diabetes association (ADA) proposed the first standard for glucose meters, recommending that accuracy be within ±10% of the reference reading for 100% of values [8]. In 1993, the ADA recommended that glucose meters demonstrated a maximal total error of ±5% for 100% of readings, partly to minimize the frequency and severity of hypoglycemia for those attempting to achieve tight glucose control [9].

Finally, the ISO 15197 norm, *i.e.* the international standard that specifies accuracy requirements of blood glucose monitoring, was published in 2003 [10]. This norm is still used as a minimum requirement for the performance of meters. The minimum acceptable accuracy of results is as follows: 95% of the individual glucose results shall fall within ±15 mg/dL (0.83 mmol/L) of the results of the manufacturer's measurement procedure for glucose concentrations <75 mg/dl (<4.2 mmol/L) and within ±20% for glucose concentrations ≥75 mg/dL (≥4.2 mmol/L). If these criteria were met, a device was considered as clinically accurate and in accordance with the norm. The ISO norm was updated in 2013.

We present here a multicentric analysis of eight blood glucose and four blood ketone meters to evaluate their respective performances in terms of precision, accuracy and hematocrit interference. This evaluation was performed according to the International Organization for Standardization (ISO) 15197 norm [10].

2. Materials and methods

2.1. Study design

Within the frame of Assistance Publique-Hôpitaux de Paris (AP-HP), a prospective multicentric assessment of the reliability of eight blood glucose monitoring systems (Freestyle Optium H) and Precision Xceed Pro (Abbott), Contour XT (Bayer), Veriopro + (Lifescan), Xpress-I and Statstrip (Nova), Accucheck Performa and Accucheck Inform II (Roche) was performed by six biochemistry laboratories in six different AP-HP hospitals.

The study followed the guidelines of good laboratory practice. Among the meters evaluated, three (Precision Xceed Pro Abbott, Statstrip Nova and Accucheck Informa II Roche) were connected to central software that aims to collect the patients and control data and to ensure the optimal follow up of such data. Among those meters, four were designed for β-ketone blood monitoring (Freestyle Optium H and Precision Xceed Pro Abbott, Xpress-I and Statstrip Nova).

All precision evaluations were performed on Quality Controls' material, whereas all other measurements were performed on venous blood collected onto lithium heparin. Samples were first assayed on point of cares meters and then (within 5 min) centrifuged (10 min, 1500 g) at room temperature (the resulting plasma contained less than 0.1% blood cells or platelets) and assayed using laboratory standardized reference methods. Samples were analyzed within 30 min. with the two devices to avoid significant glycolysis effect on glucose result.

2.2. Glucose precision evaluation

Quality control (QC) materials were assayed similarly for all blood meters as blood samples according to manufacturer's instructions and using manufacturer's QC vials.

Within-Run precision (n = 30 measurements for each QC level) was evaluated on two or three control solutions (as provided by the manufacturers), with glucose concentrations adjusted to mimic hypoglycemic, euglycemic and hyperglycemic conditions (Bayer, Lifescan, Nova, Roche) or only hypo- and hyper-glycemic conditions (Abbott), in five centres.

Between-Run precision (n = 30 measurements for each QC level) was evaluated using the same reference materials, with one to three assays each day, in five centers.

According to the ISO 15197 norm, precision was judged as acceptable when the coefficient of variation (CV) was below 7.5% for a glucose blood value higher than 4.2 mmol/L (76 mg/dL), and below 0.42 mmol/L (8 mg/dL) for a glucose blood value lower than 4.2 mmol/L (76 mg/dL).

To be considered as acceptable in our study, meters have to fit ISO 15197 norm criteria for almost 75% of all experiments.

2.3. Glucose accuracy evaluations

Accuracy evaluation of meters on venous blood samples was conducted in 5 different laboratories, enrolling for a total of about 250 patients. No pediatric sample was included in this study. To assess accuracy, the plasma glucose assay performed on a laboratory analyzer was chosen as the reference method. Briefly, samples were collected among patients to cover the following distribution: five samples with glucose values lower than 2.8 mmol/L (50.4 mg/dL), 10 from 2.8 to 5.5 mmol/L (50.4–99 mg/dL), 15 from 5.6 to 11.1 mmol/L (100.8–199.8 mg/dL), 15 from 11.2 to 16.7 mmol/L (201.6–300.6 mg/dL), and 5 higher than 16.7 mmol/L (300.6 mg/dL) [11].

In accordance with the ISO 15197 norm, to obtain samples with low glucose levels, blood samples were incubated at 37 °C to allow glycolysis to occur. On the contrary, blood samples were spiked with a hypertonic glucose solution to obtain high glucose samples. The samples were first tested on meters and then centrifuged (10 min; 1500 g; room temperature).

Central laboratory glucose precision was assessed using QC. As all the laboratories participating in the study are implied in the management of patients in hospital settings, they used QC of at least two levels at least twice a day. External evaluation of the quality, and inter-laboratory comparison of quality control results are performed regularly, as stated

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