Advantages to using capillary blood $\delta$-hydroxybutyrate determination for the detection and treatment of diabetic ketosis

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SUMMARY

Ketone body determination is indicated in all diabetic patients when the risk of ketotic decompensation exists. New methods of screening for ketosis, in particular capillary blood ketone body determination, provide analytical, technical and clinical advantages compared to the conventional ketonuria. It is proposed that a diabetic patient with hyperglycaemia (capillary blood glucose > 2.50 g.l$^{-1}$) and capillary blood ketone bodies exceeding 0.5 mmol.l$^{-1}$ requires therapeutic management. For values greater than 3 mmol.l$^{-1}$ or in case of more serious clinical symptoms, hospitalisation is indicated, considering the high probability of ketoacidotic decompensation.

The advantages of capillary blood ketone body determination including easy use, and rapid and objective results may improve management of the diabetic patient, especially in emergency situations. However, prescription by a physician of capillary blood ketone body determination should be offered to targeted populations that have a high risk of ketoacidotic decompensation, after providing education to patients that is above all aimed at preventing this metabolic complication.

In this context of determining ketone bodies in capillary blood, the term “capillary blood ketone bodies” is therefore preferable to the term “capillary blood b-hydroxybutyrate determination”. Indeed, it appears more appropriate, simple, descriptive and significant both for health-care staff and for patients.

Key-words: Ketonemia · Ketoacidosis · Diabetes · Hydroxybutyrate · Hyperglycaemia.


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RÉSUMÉ

Intérêt de l’application du dosage du $\delta$-hydroxybutyrate du sang capillaire au dépistage et au traitement de la cétose diabétique

La mesure des corps cétoniques est indiquée chez le patient diabétique dans toute situation où il existe un risque de décompensation cétosique. L’apport de nouvelles techniques de dépistage de la cétose, en particulier la mesure capillaire de la cétonémie apporte des avantages analytiques, techniques mais aussi cliniques comparativement à l’utilisation conventionnelle de la cétonurie. Ainsi, il est proposé de considérer qu’un patient diabétique en hyperglycémie (glycémie capillaire > 2.50 g.l$^{-1}$) et dont la cétonémie capillaire dépasse 0.5 mmol.l$^{-1}$ impose une intervention thérapeutique. Pour des valeurs supérieures à 3 mmol.l$^{-1}$ ou dans le cas d’un tableau plus défavorable, l’hospitalisation est indiquée compte tenu d’une probabilité élevée de décompensation acido-cétosique.

Les avantages de la mesure de cétonémie capillaire en termes de maniabilité, de rapidité d’obtention et d’objectivité des résultats sont susceptibles d’améliorer la prise en charge du patient diabétique, en particulier dans un contexte d’urgence. Cette prescription médicale de la cétonémie capillaire doit cependant être proposée à des populations ciblées à risque élevé de décompensation cétosique et après un travail d’éducation visant avant tout à la prévention de cette complication métabolique…

Dans ce contexte de mesure des corps cétoniques au niveau capillaire, la dénomination « cétonémie capillaire » est alors préférée au terme « mesure du b-hydroxybutyrate capillaire ». Elle apparaît en effet plus appropriée, simple, descriptive et significative tant pour le personnel soignant que pour les patients.

Mots-clés : Cétonémie · Céto-acidose · Diabète · Hydroxybutyrate · Hyperglycémie.

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Diabetes is a chronic disease which is associated with serious complications. Acute metabolic complications such as ketoacidosis can be differentiated from chronic complications promoted by poor diabetic control and by a high incidence of hyperglycaemic episodes [1]. Absolute or relative insulin deficiency can result in ketosis. If left untreated, the latter can progress to ketoacidosis, a serious and sometimes fatal pathological condition. In adults in France in 2002, the estimated number of episodes of ketoacidosis was 10,000 to 12,500 per year [2]. Mortality associated with ketoacidosis is between 3 and 4% of episodes [3] in industrialized countries. The situation is of even greater concern in children in whom ketoacidosis is the leading cause of mortality and morbidity associated with diabetes worldwide. This is due mainly to acute cerebral oedema, a very serious complication in children [4]. Currently, the only way of reducing such morbidity and mortality is to prevent the ketoacidosis, whether occurring as an initial event or in a child known to have type 1 diabetes mellitus.

In adults, the vast majority of patients treated for ketoacidosis are those in whom diabetes has already been diagnosed. Only 10% of patients with ketoacidosis are cases that lead to the discovery of diabetes [5]. This is not true in children, where ketoacidosis in paediatric patients is the most frequent circumstance in which diabetes is revealed (half of all cases in France). Prevention of serious cases of hyperglycaemia and ketoacidosis involves regular self-monitoring of blood glucose by patients in conjunction with monitoring of urinary ketone bodies.

However, in its latest recommendations on the “Test of glycaemia in diabetes”, in 2004, the American Diabetes Association (A.D.A) [6] has emphasized the usefulness of an alternative method: “Health care professionals should be aware, however, that currently available urine ketone tests are not reliable for diagnosing or monitoring treatment of ketoacidosis. Blood ketone testing methods that quantify, ß-hydroxybutyric acid, the predominant ketone body, are available and are preferred over urine ketone testing for diagnosing and monitoring ketoacidosis. Home test for ß-hydroxybutyric acid are available”.

In fact, new methods are now available for screening for ketone bodies, and they have the same practical advantages as those that measure capillary blood glucose. In a manner similar to the assessment of automatic digital display analyzers for measuring blood glucose (as a replacement for the urinary method), an update on the measurement of capillary blood ketone bodies, compared with conventional urinary methods of measurement, appears to be necessary.

With the aim of formulating a protocol of use of this new method, guidelines in the standardized protocol of the Consensus Conference have been followed [7]. The various issues were listed by a working party comprised of Drs. L. Monnier, C. Le Dévéhat, Mrs D. Durain and JP Le Floch, spokesman. They were submitted to another group of independent experts made up of Drs B. Bauduceau, R. Bresson, A. Cuperlier, C. Delcroix, C. Fermon, V. Melki, E. Mosnier-Pudar, P. Taboulet and N. Tubiana Rufi and Prof B. Guerci, moderator.

Discussions were conducted by Prof. B. Guerci and Dr JP. Le Floch. Prof. H. Hanaire-Broutin was the chairwoman and coordinator of this entire study.

**Indications for ketone body determination in ambulatory practice and in the hospital**

Measurement of ketone bodies is indicated in a diabetic patient in all cases where the risk of ketotic decompensation exists [8]. It is essential to educate the diabetic patient, in particular one who is in a high-risk situation, or who belongs to a high-risk population, in the early detection of any rise in blood ketone bodies in the context of self-monitoring of blood glucose management.

The wide range of contexts which carry a high risk of decompensation means that it is not possible to present a comprehensive list of them. The concomitant occurrence of unusual hyperglycaemia and of a context or symptoms considered by clinicians to carry a risk of ketotic decompensation (i.e. fever, vomiting, etc) may warrant ketone body determination.

Defining this threshold of hyperglycaemia is necessarily arbitrary, all the more so since references obtained from published reports do not propose a consensus value for blood glucose (2.2 – 3 g.l^-1) [6, 9, 10]. For the purpose of simplification and by referring to the most widely recognized values, a blood glucose level greater than 2.50 g.l^-1 will be used in the context of the detection of ketosis [8, 10]. This threshold value can vary depending on individual cases and/or populations and is left to the physician’s judgment.

**In ambulatory practice**

- Patients with type 1 diabetes mellitus in a situation of hyperglycaemia and exposed to an established risk. In particular, this involves:
  - Children and teenagers, [10, 11, 12, 13]
  - Patients treated with an external or implantable insulin pump, [6, 10, 14-16]
  - Pregnant diabetic women or women with gestational diabetes [8, 17-19]
  - Patients with type 1 or type 2 diabetes, in cases of symptomatic and/or unusual hyperglycaemia (capillary blood glucose > 2.50 g.l^-1) and one or more factors for lack of control [10]:
    - Révélation of type 1 diabetes, in particular in children or insulin-requiring diabetes, in particular in the elderly,
    - Infection,
    - Stroke,
— Alcohol and substance abuse,
— Pancreatitis,
— Myocardial infarction,
— Trauma,
— Discontinuation of insulin therapy or non-compliance,
— Treatment with drugs that affect carbohydrate metabolism, i.e. corticosteroids, thiazide diuretics, and sympathomimetic agents, in particular dobutamine and terbutaline, etc.,
— Stress-related psychological disorders, complicated or uncomplicated by an eating disorder,
— Behavioural disorders in young patients that can lead to non-compliance with insulin therapy: fear of gaining weight, fear of hypoglycaemia, rebellion against authority, and stress generated by a chronic disorder.

**In the hospital setting**

This applies to the following:
— All cases of hyperglycaemia (as previously defined by a blood glucose value of greater than 2.50 g/l) in combination with an acute clinical condition: emergency situation, post-operative period, intensive care, major dehydration, oligoanuria, etc.,
— cases of hyperglycaemia described in ambulatory practice when a diabetic patient is hospitalised.

**Advantages and disadvantages of new available methods (allowing capillary blood β-OHB determination) compared to the measurement of ketonuria for the diabetic patient and for the healthcare provider**

In analytical terms:
Tests with nitroprusside provide a semi-quantitative estimate of aceto-acetate in the urine while capillary blood ketone body determination measures β-hydroxybutyrate (β-OHB), the main ketone body in the blood, and reflects insulin deficiency and the risk of ketosis in the diabetic patient [20]. Lastly, capillary blood ketone body levels are not subject to interference from medicinal products, unlike the measurement of ketonuria, which, firstly is sensitive to acetyl-cysteine and/or captopril [21, 22] and, secondly, yields a negative result in the event of contact with ascorbic acid. Thus, it provides the clinician and patient relevant information.

In clinical practice:
Capillary blood ketone body determination differs from ketonuria determination in terms of the technical procedure used and in interpretation of results.

**Technical procedure**

Capillary blood ketone body determination can be done quickly and involves a procedure similar to capillary blood glucose measurement. Thus, it does not require additional training either for the healthcare provider or for the diabetic patient, apart from that of standardization. It is more practical and more comfortable for diabetic patients who show a marked preference for this method compared to measuring ketonuria, in particular among children and teenagers [11]. The lack of need to collect urine is an important component in the improvement of quality of life. The result, in particular in ambulatory patients, appears more objective and more readable for the patient, and should improve compliance with and confidence in self-monitoring. L Laffèl et al. [23, 24] examined the ambulatory aspect of the use of ketone body determination and concluded that the percentage of patients who checked their ketone bodies on days of blood glucose imbalance over a 6-month period was significantly higher in the “blood ketone body” group than in the “ketonuria” group (90.8% vs 61%) (P < 0.001).

On the other hand, this test requires a larger drop of blood (5 µl) than that usually necessary for capillary blood glucose determination and requires that subjects who were shown how to take such measurement and are used to monitoring ketone bodies in the urine make a change in their habits.

For healthcare staff, this method offers the advantage of producing results that are much faster since it is not necessary to wait and collect urine. Several authors have emphasized that measurement of β-OHB is preferable because it does not require any additional work in a hospital department [25, 26]. This method is reliable because it is performed by the healthcare provider who can verify the origin of the sample. The measurement can also be readily repeated. However, in the event that use of the analyzer is shared (if it has been certified for such use), the healthcare professional must use perfect technique in conducting the test, in order to limit risks of cross-contamination from one patient to another. Lastly, it should be noted that the opening of a new box of measuring electrodes requires a standardization to be performed, thus requiring that prescribing healthcare professionals (physicians) and healthcare staff who perform monitoring in the hospital setting (nurses) make adjustments in their work habits.

**Technical aspects of measurement**

The risk of making a mistake in reading capillary blood ketone body determination, and thus in interpretation, is reduced due to the fact that a numerical value is displayed digitally on the analyzer screen. The speed and accuracy of the ketone body determination measured allows prompt corrective therapeutic measures to be implemented that are better suited to the clinical context of the emergency [27]. It appears necessary to verify that the accuracy of the device is maintained by technical monitoring such as quality control in everyday use identical to that set up for the use of capillary blood glucose measurements. A study of the agreement of results with those obtained by the reference method must
be done both in ambulatory practice, as well as in the hospital setting. Byrne et al. [28] have demonstrated that the currently available method of capillary blood ketone body determination (Optium™ B-ketone, Abbott laboratories) is accurate and precise.

In clinical terms:

Umpierrez et al. [29] have observed that the urinary test with nitroprusside remains positive more than 24 hrs after resolution of an episode of ketoacidosis (bicarbonates > 18 meq/l- pH of venous blood > 7.3) in over half of patients studied. Wiggam et al. [25] observed that, in patients with ketoacidosis treated with IV insulin, measurement of blood ketone bodies together with blood glucose monitoring resulted in a faster return of B-OHB to concentrations of less than 0.5 mmol/l than in the “blood glucose monitoring only” group (5.9 ± 0.8 vs 21.8 ± 3.4 hrs; P = 0.004). These authors observed that normal blood glucose occurred earlier than normal blood ketones, but that it is not an adequate marker of the patient’s return to normal metabolic status. Real-time monitoring of ketonemia appears to be an essential condition for initiating appropriate insulin therapy. The intermediate results of an ongoing, open-label, randomised study conducted by Dr Mosnier-Pudar [26] point in this same direction. In this study of diabetic patients with ketosis, a treatment adjusted according to ketonemia in 8 patients was compared to conventional management based on the monitoring of ketonuria in 8 control subjects. The episode of ketosis was resolved more quickly in the group evaluated by means of ketonemia than in the control group (mean duration of episode of ketosis: 2hrs28 ± 0hrs52 [median 2hrs05] vs 10hrs42 ± 10hrs32 [4hrs45]).

Guerci et al. [16] have emphasized the early aspect of diagnosis of ketosis when a capillary blood measurement of E-Ketone is performed as compared to ketonuria in patients with type 1 diabetes after accidental discontinuation of insulin infusion with an external pump. Furthermore, urinary ketone bodies persist for a long time after resolution of the episode. The authors describe this difference as “a delay in diagnosis” considered “significant between plasma ketonemia and ketonuria”. Taboulet et al. [30] have reported the same sensitivity (89%) of urinary and capillary blood tests in the diagnosis of severe ketosis in 173 subjects, but a significantly higher specificity of ketonemia (99%) (P < 0.0001) than that of ketonuria (84%).

**Interpretation of a capillary blood B-hydroxybutyrate value:**

**Threshold values or ranges for normalcy, values for intervention**

Ideally, the definition of normal values or values for intervention according to blood ketones should be based on controlled studies currently available. Studies conducted by Umpierrez [29] et al. have reported resolution of episodes of ketoacidosis (bicarbonates > 18 meq/l- pH venous blood > 7.3) whenever B-OHB concentrations are less than 0.5 mmol/l but never when they exceed 1.1 mmol/l.

While awaiting additional results, it has been proposed to use thresholds based on the experience reported by several teams, in particular, in an emergency situation [30]. In all cases, it would not be possible to interpret a capillary blood ketone body value without comparing it to concomitant blood glucose levels and to the outcome of blood glucose and ketone body values over time. Interpretation of clinical context is also essential, in particular in children: lengthy fasting, a concomitant disorder, clinical symptoms [13].

By consensus, a capillary blood ketone body value of greater than 0.5 mmol/l is considered “abnormal”. This figure is a threshold value with regard to the risk of decompensation [23]. Consequently, in a hyperglycaemic diabetic patient treated with insulin (capillary blood glucose > 2.50 g/l) and whose capillary blood ketone body determination is greater than 0.5 mmol/l, intervention is necessary by means of increased monitoring with repetition of measurements, or even enhanced therapy.

In populations at specific risk for ketoacidotic decompensation, this threshold value can be lower. Therefore, patients treated with an insulin pump could benefit from intervention starting from a blood ketone body level of greater than 0.3 mmol/l, in particular if this is a postprandial determination [15]. In pregnant women, ketone body levels will be interpreted depending on the stage of the pregnancy. Specific studies are necessary to define standardized conduct for intervention. For ketonemia measured between 0.5 mmol/l and 3 mmol/l, corrective measures are based on a subcutaneous injection of fast-acting insulin, or a fast-acting insulin analogue, according to established protocols, and on the initiation of hourly monitoring of ketonemia until resolution of the episode. However, certain clinical contexts can warrant hospital management, in particular if the cause of decompensation persists or cannot be clarified promptly (Tables I and II).

Above a blood ketone body level of 3 mmol/l, and even if hyperglycaemia is moderate, ketoacidosis is confirmed and appropriate emergency management must be initiated [30]. For these values greater than 3 mmol/l or in the case of a more unfavourable situation, hospitalization will be required to confirm the diagnosis of ketoacidosis, to perform an appropriate assessment and to initiate necessary corrective treatment procedures, if needed with an IV infusion of insulin until the episode resolves.

The episode of ketosis will be considered as resolved when the blood ketone body level has returned below the threshold value for intervention, i.e. a capillary blood ketone body level of less than 0.5 mmol/l. These values and the therapeutic measures are provided for informational purposes, based on actual data from the literature.
This new method of blood ketone body determination carries a higher cost than the urinary method of measurement. This is why in France, for example, the health authorities have limited its reimbursement to populations of diabetic patients who are most vulnerable to the risks of ketosis and ketoacidosis. This thus involves patients with type 1 diabetes with an insulin pump, children and teenagers up to 18 years of age and pregnant diabetic women [31].

Lastly, with regard to a semantic issue, to facilitate the use of capillary blood ketone body determination, it should be designated not only by a descriptive and scientifically correct term, but also by a term that can be readily understood by everyone.

The term “cétonémie capillaire” [“capillary blood ketone bodies”] seems the most appropriate. It is simple, descriptive and significant. It continues along the lines of the use which has endorsed the terms “cétonurie” [“ketonuria”] or “glycémie capillaire” [“capillary blood glucose”], now commonly used by health-care staff and diabetic patients. Thus, it is the perfect translation of the term “ketonemia” or “blood ketone bodies” frequently used in the English-language medical literature. By extrapolation from the area of blood glucose monitoring, we now can refer to “self-monitoring of ketone bodies” or “self-surveillance of ketone bodies”.

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References


