What are capillary blood ketone levels in type 1 diabetic patients using CSII in normal conditions of insulin delivery?

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SUMMARY
Objective: The aim of the study was to determine the normal level of capillary ketonemia in type 1 diabetic patients on continuous subcutaneous insulin infusion (CSII).

Research design and methods: A total of 36 type 1 diabetic patients treated by external pump were studied for 2 to 3 weeks. Patients were instructed to self monitor capillary glucose and capillary ketone bodies at least 4 times per day with a handheld Medisense Optium meter and check for urinary ketone bodies in the morning and when blood glucose exceeded 2.5 g/l with a semiquantitative test. Data were collected and analysed for each period of time defined as the time interval between two changes of the infusion site. A period was considered “normal” when no problem causing any impairment in insulin delivery was detected.

Results: 186 periods of 2.1 ± 0.9 days were recorded; 119 were considered normal. 1281 coupled values of glucose and betahydroxybutyrate were analysed during the so called normal periods. Mean percentage of ketonemia of 0, 0.1, 0.2, and 0.3 mmol/l were 81.3%, 13%, 3.7% and 2% respectively whereas mean glucose level (g/l) was 1.49 ± 0.7, 1.48 ± 0.7, 1.59 ± 0.8 and 1.89 ± 0.9 respectively. Only 0.9% of betahydroxybutyrate values were ≥ 0.3 mmol/l when blood glucose exceed 2.5 g/l.

Conclusion: Our study indicates that ketonemia self monitoring can be a valuable tool to screen insulin deficiency in patients on CSII with a low risk of false positive if we consider a threshold of 0.3 mmol/l for ketone bodies.

Key-words: Capillary ketonemia · CSII · Ketoacidosis.

RéSUMÉ
Quel est le niveau des corps cétoniques en sang capillaire chez les diabétiques de type 1 traités par pompe à insuline externe en conditions normales de délivrance d’insuline ?

Objectif : L’objet de cette étude était de déterminer le niveau normal des betahydroxybutyrates chez des patients diabétiques de type 1 traités par pompe externe et lispro.

Méthodes : Trente-six patients ont été recruté et devaient réaliser, durant 2 à 3 semaines, une mesure des betahydroxybutyrates après chaque glycémie à l’aide d’un lecteur Medisense Optium et une recherche de corps cétoniques urinaires en cas de glycémie > 2.5 g/l. Des périodes de traitement, où tout incident susceptible d’entraîner une carence en insuline pouvait être écarté, dites périodes normales, ont été sélectionnées.

Résultats : Cent quatre-vingt-six périodes de 2.1 ± 0.9 jours ont été analysées dont 119 étaient considérées normales. Mille deux cents quatre-vingt-six couples de valeurs de glycémies et de betahydroxybutyrates ont été obtenus au cours des périodes normales. Les pourcentages respectifs de cétonémie égales à 0, 0,1, 0,2 et 0,3 mmol/l étaient de 81,3%, 13%, 3,7% et 2% alors que les taux moyens de glycémies respectifs étaient de 1,49 ± 0,7, 1,48 ± 0,7, 1,59 ± 0,8 et 1,89 ± 0,9 g/l. Seules, 0,9 % des valeurs de betahydroxybutyrates étaient ≥ 0,3 mmol/l lorsque les glycémies étaient > 2,5 g/l.

Conclusion : L’autosurveillance de la cétonémie pourrait permettre un dépistage précoce des situations de carence en insuline lors du traitement par pompe, avec un risque faible de faux positifs, si l’on considère que la cétonémie est élevée dès qu’elle dépasse la valeur seuil de 0,3 mmol/l.

Key-words : Cétonémie capillaire · Pompe à insuline · Acidocétose.

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The need to improve the quality of life of diabetic patients mainly by reducing the risk of long term complications [1] lead to the widespread use of CSII. Nevertheless, CSII is associated with an increased risk of diabetic ketoacidosis (DKA) related technical insulin output failure especially when short acting insulin analogs are used [2-5]. Consequently, modern diabetes management requires intensive self monitoring of blood glucose levels coupled with urinary ketone testing. However the latter is associated with poor patient compliance [6] and delayed time to diagnosis of DKA [7, 8] stressing the need of a “real time” evaluation of ketosis.

The recent introduction of a method for measuring 3 beta hydroxybuturate in capillary blood allows quantitative analysis of the acute metabolic derangement. Recent studies underlined the accuracy of this new technique and demonstrated its superiority to that of ketone testing in urine for early detection of ketosis [9, 10]. However, the currently accepted normal values of blood ketones were determined by venous sampling in patients on multiple daily injections (MDI) [11]. Therefore a threshold for normal capillary ketones need to be clearly defined in type 1 diabetic patients on CSII.

The aim of our study was to determine the normal level of capillary ketone bodies specifically beta hydroxybuturate in type 1 diabetic patients on intensive insulin therapy using CSII and a short acting insulin analog.

**Research design and methods**

**Patients**

A total of 36 type 1 C-peptide negative diabetic patients were recruited. Patients were on CSII with insulin lispro (Humalog U100 Lilly France, St Cloud) via an external pump (Minimed 506, 507, 507 C, 508 Medtronic Minimed, Northridge,CA) or Htrion C100, V100, plus D100, plus V100 (Disetronic Medical Systems, Burgdorf, Switzerland) and a catheter polyfin QR or Sofset QR (Minimed) or Rapid and Tender (Disetronic Medical systems Burgdorf, Switzerland). Infusion site and catheter were changed every 2 to 3 days. All patients performed blood glucose self monitoring at least 4 times per day and a daily surveillance of urinary ketones. Body weight was stable during the last month prior to the study and HbA1c (HPLC, Menarini, Switzerland) was measured at inclusion.

Exclusion criteria included impaired renal function (creatinin clearance < 70 ml/min), hypocaloric diet that could induce weight loss and ketogenesis, pregnancy and breast feeding, any medication that would interfere with urinary ketones testing such as acetylcysteine, captopril, Mesna, corticosteroids, Dimercaprol, penicillamine, or alcohol abuse. Subjects were also excluded if they had participated in another research study within the last month.

The study protocol was approved by the ethical committee of Toulouse (France) and all subjects gave their informed consent.

**Study protocol**

After recruitment, the study included 2 visits. At visit 1 (week 0) subjects were provided with a “Medisense Optium” meter (Abbot France-division Medisense, Rungis France) which is a handheld dual glucose and ketone sensor and were instructed to self monitor capillary blood glucose and ketones at least 4 times a day (before each meal and 2 hours after one of the 3 meals) and check for ketones in the morning urine by a semiquantitative test (Ketodastix, Bayer Diagnostics Puteaux France) and when blood glucose exceeded 2.5 g/l. Patients were given a note book to record glycermia, ketonemia and ketonuria when changing or removing the catheter. They were also requested to fill out a questionnaire assessing the reason for which they had prematurely removed the catheter (hematoma, pain or alarm pump set off), any abnormal finding at the infusion skin site, and catheter patency when removed.

At visit 2 (week 2 to 3) the memory meter was downloaded on a PC computer by means of the Link plus 2.0 software (Medisense Rungis, France). Capillary glucose and ketone values since visit 1 were analyzed. Data from the questionnaire regarding intercurrent events such as ketonuria, skin abnormalities at the infusion site or catheter during the study period were collected.

A “period” was defined as the time interval between two changes of the catheter infusion site (period of 2 to 3 days).

A “normal period” (i.e adequate insulin delivery achieved) was defined by the following criteria: absence of ketone bodies in the urine confirmed every morning and when glucose level exceeded 2.5 g/l, normal aspect of the skin at the infusion site, and catheter patency when removed.

Unselected periods were those where compliance for monitoring urinary ketones were unsatisfactory or when ketone bodies were detected in the urine or when a technical pump failure, catheter obstruction, any abnormality at the infusion site were recorded. It is worth noting that in these unselected periods abnormal insulin delivery could not be confirmed nor excluded and thus any comparison between the so called “normal periods” and unselected periods would not be beneficial in term of specificity and sensitivity for determining the threshold of normal capillary ketonemia.

Only data of “normal periods” were kept for analysis to define normal capillary ketonemia.

Results are given as mean ± SD, median and range.

**Results**

Out of the total 36 recruited subjects, one was excluded because of non compliance to the study protocol, another had a positive C-peptide level and was diagnosed as Latent...
Autoimmune Diabetes in Adults (LADA) and a third patient was lost to follow up. Data from the remaining 33 subjects were analysed (the main clinical and biochemical characteristics of these patients are summarized in Table I).

At visit 1 (week 0) self monitoring of blood glucose was satisfactory as testing was done 5.3 ± 1.3 times a day ranging between 3.4 and 7.4 times per day. Morning ketonuria was checked systematically in 72.2% of patients and in 87.9% when glucose rose above 2.5 g/l.

During the study, 2400 self monitoring of blood glucose were done. One hundred and eighty six periods of 2.1 ± 0.9 days were recorded. 119 were considered uneventful « normal periods ». One thousand four hundred and sixty glycemic controls were realised during these normal periods, out of which 1281 (88%) were coupled to betahydroxybutyrate measurements and then subsequently analysed. Median level of betahydroxybutyrate was 0.0 mmole/l (0.0 to 0.7) for a mean glucose level of 1.47 ± 0.69 g/l (0.36-4.26).

In 1041 measurements out of 1281 (81.3%), 166 (13%), 48 (3.7%) and 26 (2%) ketonemia level was 0, 0.1, 0.2, 2 0.3 mmole/l respectively whereas mean glucose level (g/l) was 1.49 ± 0.7, 1.48 ± 0.7, 1.59 ± 0.8 and 1.89 ± 0.9 respectively. 1255 values of betahydroxybutyrate out of 1281 measurement (98%) were less than 0.3 mmole/l (Fig 1).

In 4 measurements (1.6%), 18 (2.7%), and 4 (1%) betahydroxybutyrate values were 2 0.3 mmole/l depending on measurement hours, fasting, pre and 2 hours postprandial respectively (Fig 2).

Only 0.9% of betahydroxybutyrate value were 2 0.3 mmole/l when blood glucose exceeded 2.5 g/l.

**Conclusion**

Currently the widespread use of CSII with short acting insulin analogs provides the best therapeutic option to achieve near normal blood glucose control [12-15]. However, ketosis may develop earlier because of the pharmacokinetic properties of the insulin used [16] and pump related failures such as catheter obstruction, needle dislodgement, or leakage at the infusion site [17-19]. Consequently an early detection of ketone bodies in order to prevent acute metabolic decompensation and hazardous DKA should be an integral part of the monitoring program for all type 1 diabetic patients on CSII.

It is generally agreed that the normal level of plasma ketone bodies is less than 0.5 mmole/l whereas hyperketonemia is defined as a level above 1 mmole/l and DKA > 3 mmole/l [20]. These levels of ketonemia were established according to observational studies in diabetic patients on (MDI) [11]. However it is well known that insulin pump provides a better physiological delivery of insulin than MDI especially during the night time period circumventing peaks and nadir insulin blood levels. Consequently the level of normal capillary ketones in this population should be theoretically lower than that encountered in patients on MDI. Moreover in a recent study by Guerci et al., capillary blood Beta OH butyrate levels were highly correlated with plasma Beta OH butyrate after CSII interruption in type 1 diabetic patients, but the level of capillary ketones remained significantly lower than the level measured in the plasma [10]. These discrepancies underlined the need for a definition of a threshold of capillary ketosis in type 1 diabetic patients on CSII.

Our study demonstrates that normal Beta OH butyrate capillary levels in type 1 diabetic patients on CSII ranks between 0.0 and 0.2 mmole/l, levels found in 98% of the cases independently of the time measurement (fasting, pre or postprandial). Nevertheless, 2% of the cases had a level of beta OH butyrate 2 0.3 mmole/l, out of which 0.9% had

<p>| Table I |</p>
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<th>Patient’s clinical and biochemical characteristics.</th>
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<td>Sexe (F/M)</td>
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<td>Age (years)</td>
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<td>BMI (kg/m²)</td>
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<td>Diabetes duration (years)</td>
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<td>Mean duration of CSII treatment (years)</td>
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<td>HbA1c (%; normal range: 4-6)</td>
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**Figure 1**
Mean capillary ketonemia level (mmole/l) in type 1 diabetic patients on CSII 98% of normal values of betahydroxybutyrate levels are less than 0.3 mmole/l.

**Figure 2**
Percentage of Betahydroxybutyrate measurements 2 0.3 mmole/l according to the time measurement.
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References