A morning dose of insulin glargine prevents nocturnal ketosis after postprandial interruption of continuous subcutaneous insulin infusion with insulin lispro

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Abstract

Aim. – The aim of this crossover trial was to evaluate the potential of partial substitution of basal insulin with glargine, administered once daily in the morning, to protect against nocturnal ketosis after postprandial interruption of continuous subcutaneous insulin infusion (CSII).

Methods. – Seven patients with type 1 diabetes received 4 weeks of treatment with insulin lispro, administered by CSII, and 4 weeks of treatment with CSII and a partial basal replacement dose of insulin glargine administered in the morning. On day 28 of each treatment phase, patients were admitted to the research unit where dinner was served and their usual dinner insulin bolus dose given, after which CSII was discontinued at 7 pm. Plasma (p) \(\beta\)-hydroxybutyrate and p glucose were measured every hour for 12 h thereafter.

Results. – Plasma \(\beta\)-hydroxybutyrate at 7 pm was 0.16 ± 0.05 and 0.13 ± 0.07 mmol/l with and without glargine, respectively, and increased to 0.17 ± 0.10 and 0.60 ± 0.3 mmol/l within 6 h (\(P = 0.02\)). Plasma glucose increased without glargine, from 8.6 ± 2.9 to 21.1 ± 3.0 mmol/l (\(P = 0.003\)), but did not rise significantly following glargine: 13.6 ± 4.7 vs. 12.6 ± 5.6 mmol/l; \(P = 0.65\).

Conclusions. – Partial replacement with a morning dose of insulin glargine protects against the development of ketosis for as much as 12 h after postprandial interruption of CSII. This treatment strategy could, therefore, be useful for patients who are prone to ketosis but, for other reasons, are deemed suitable for CSII.

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Résumé

Une dose d’insuline glargine administrée le matin prévient la cétose nocturne après interruption après le dîner de la perfusion sous-cutanée continue d’insuline lispro (CSII)

Objectif. – Le but de cet essai croisé était d’évaluer la possibilité de substituer partiellement l’insuline basale avec une injection matinale d’insuline glargine, en prévention de la cétose nocturne en cas d’interruption de CSII après le dîner.

Méthodes. – Sept diabétiques de type 1 ont suivi pendant quatre semaines un traitement à l’insuline lispro administrée par CSII et quatre semaines de traitement avec CSII et une dose de base partielle de remplacement d’insuline glargine administrée le matin. Le 28\textsuperscript{e} jour de chaque phase de traitement, les sujets ont été admis dans l’unité de recherche. Ils ont reçu leur dîner et leur bolus habituel d’insuline. La CSII a ensuite été interrompue à 19 heures. Les concentrations plasmatiques de \(\beta\)-hydroxybutyrate et de glucose ont été mesurées toutes les heures pendant les 12 heures suivantes.

Résultats. – Les concentrations plasmatiques de \(\beta\)-hydroxybutyrate à 19 heures étaient de 0,16 ± 0,05 et de 0,13 ± 0,07 mmol/l, respectivement avec et sans glargine, montant jusqu’à 0,17 ± 0,10 et 0,60 ± 0,3 mmol/l six heures plus tard (\(P = 0,02\)). Les concentrations plasmatiques de glucose ont augmenté sans glargine de 8,6 ± 2,9 à 21,1 ± 3,0 mmol/l (\(P = 0,003\)), mais n’ont pas augmenté d’une façon significative après glargine : 13,6 ± 4,7 vs 12,6 ± 5,6 mmol/l (\(P = 0,65\)).
Continuous subcutaneous insulin infusion (CSII) is a well-established therapeutic regimen with a potential to mimic the physiology of basal insulin secretion beyond that of multiple daily injections (MDI). In the diabetes control and complications trial (DCCT), as much as 40% of patients were at times on CSII, the superiority of which over MDI has been demonstrated by recent meta-analyses [1,2]. The properties of rapid-acting insulin analogs are thought to be particularly appropriate for CSII therapy, and the use of insulin analogs in CSII provides a further significant improvement in glycaemic control compared with regular insulin [3,4]. However, the use of insulin analogs in CSII carries a significant risk of ketosis within hours if the delivery of insulin is interrupted [5–7]. Unfortunately, the currently available technology does not provide reliable systems to detect such interruptions that, at night, may remain undiscovered for several hours.

The addition of an injection of a long-acting insulin analog to CSII therapy may have the potential to prevent ketosis, as indicated by a recently published case report where partial basal insulin replacement with glargine during CSII was successful [8]. We addressed this issue further in an open, controlled, crossover trial to assess the potential of partial substitution of basal insulin with glargine, administered once daily in the morning, to protect against nocturnal ketosis after intentional interruption of CSII.

1. Research design and methods

Seven C-peptide-negative patients with type 1 diabetes (three women and four men, HbA1c 7.4 ± 0.6, age 39 ± 15, BMI 25.3 ± 2.2) participated in an open, randomized, crossover study. All subjects had been treated with CSII for at least 12 months, and none had evidence of impaired renal function, macrovascular complications of diabetes or other chronic disease. The protocol was approved by the Ethics Committee of the Karolinska Institute, and all participants gave their written informed consent.

The patients received 4 weeks of treatment with insulin lispro (Humalog; Eli Lilly, Indianapolis, IN) administered by an external pump (MiniMed, Medtronic), and 4 weeks of treatment with CSII and a partial basal replacement dose of insulin glargine (Lantus; Aventis, Bridgewater, NJ) administered in the morning, corresponding to the total basal insulin dose minus 2–4 units per day to prevent crystallization of insulin in the pump catheter [8]. Between the two phases of the study was a 1-week washout period.

On day 28 of each treatment phase, patients were admitted to the research unit where dinner was served. They were given their usual dinner insulin bolus dose, after which CSII was discontinued at 7 pm. Plasma (p) β-hydroxybutyrate and p glucose were measured every hour throughout the evening and night. Serum bicarbonate and electrolytes were analyzed every 4 h. CSII was recommended when p β-hydroxybutyrate reached 2 mmol/L or, at the latest, 12 h after interruption of CSII.

Statistical analyses were performed using the JMP software, version 3.1.5; SAS Institute, Cary, NC. Data are presented as means ± SD, and P < 0.05 was considered statistically significant. Differences between treatment with or without partial replacement of glargine were assessed using a two-tailed Student’s t-test.

2. Results

Plasma β-hydroxybutyrate at 7 pm was 0.16 ± 0.05 and 0.13 ± 0.07 mmol/l with and without glargine, respectively, and increased to 0.17 ± 0.10 and 0.60 ± 0.3 mmol/l within 6 hours (P = 0.02) (Fig. 1). Throughout the night, p β-hydroxybutyrate increased further among the controls and CSII was, thus, recommenced in three patients after 7 to 10 h. The remaining four patients reached a p β-hydroxybutyrate level of 1.58 ± 0.24 mmol/l after 12 h. Basal levels of p β-hydroxybutyrate were maintained for 12 hours when glargine was used (0.26 ± 0.15 mmol/l; P = 0.22).

![Fig. 1. The development of P-b-OHB with glargine (open circles) and without glargine (filled circles) and P-glucose with glargine (open triangles) and without glargine (black fences) after interruption of CSII. *P < 0.05, **P < 0.01.](image-url)
Plasma glucose increased without glargine, from 8.6 ± 2.9 to 21.1 ± 3.0 mmol/l (P = 0.003), but did not rise significantly following glargine: 13.6 ± 4.7 vs 12.6 ± 5.6 mmol/l (P = 0.65). Serum bicarbonate decreased from 23.7 ± 0.47 to 21.0 ± 0.58 (P = 0.0005) without glargine, but did not change significantly following glargine.

3. Conclusion

In the early years of insulin pump therapy, diabetic ketoacidosis (DKA) was a growing problem; the major cause was failure of insulin delivery from the infusion set [9]. Yet, the increased risk of DKA was not found in studies after 1993 [10]. It is thought that this improvement was due to more efficient insulin pumps and to more stringent patient education [11] as well as better patient selection. According to data from several countries, there is a current trend towards an increasing use of CSII and, in this case, it may be that patients who previously were not considered candidates for CSII may have the option of an insulin pump. Insulin glargine was introduced in Sweden a few years ago and is currently being used by an increasing number of patients, constituting approximately 40% of the basal insulin prescribed in the country. It has been demonstrated to provide a continuous supply of insulin with no pronounced peak over a 24-h period [12] and to lower the risk of nocturnal hypoglycaemia during MDI treatment compared with NPH insulin [13]. MDI with glargine and CSII, both using lispro as meal insulin, have been shown to equally improve metabolic control and to reduce severe hypoglycaemia in patients with type 1 diabetes who are not satisfactorily controlled with MDI and NPH as basal insulin [14]. However, the duration of the effect of glargine has been a topic of some debate as data have accumulated to indicate that administration twice daily is needed in up to 30% of patients with type 1 diabetes to control glycaemia [15]. Little is known of the development of ketosis in insulin treatment strategies based on insulin glargine.

In this study, we have convincingly demonstrated that partial replacement with glargine during treatment using CSII with lispro protects against the development of ketosis for as long as 12 h after postprandial interruption of CSII and 24h after injection of insulin glargine. We assessed the effect of insulin glargine in the nocturnal period as this is a particularly vulnerable time for the development of ketoacidosis [16]. This treatment strategy may be useful for patients who are prone to ketosis, but who, for other reasons, are deemed suitable for CSII at critical periods, such as CSII-treated female diabetics during pregnancy, when ketoacidosis with CSII has been reported to provoke intrauterine fetal death [17,18]. However, the long-term consequences of such a treatment strategy requires further exploration.

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