

Continuous intraperitoneal insulin infusion (CIPII) for type 1 diabetes: Effective therapy but a case of bad timing?

J.A.M.J.L. Janssen

Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands, tel: +31(0)10-7033975, fax: +31(0)10-7033268, email: j.a.m.j.l.janssen@erasmusmc.nl

In healthy subjects, insulin secreted by the pancreas is transported to the liver where a relevant amount (30-80%) is retained and degraded.¹ The remaining insulin bypasses the liver and reaches the peripheral tissues through the systemic circulation. As a consequence, in healthy subjects the liver/peripheral tissue insulin concentration ratio ranges from 3:1 up to 9:1 during insulin secretion bursts.² In type 1 diabetic patients administration of exogenous insulin is critical to achieve acceptable metabolic control. However, normal physiology is not restored by the standard intermittent subcutaneous (SC) insulin administration or continuous subcutaneous insulin infusions (CSII): with these two treatment options insulin will arrive at the peripheral tissues and the liver in similar concentrations.² This results in relative peripheral tissue hyperinsulinaemia and relative liver hypoinsulinaemia, which contrasts with the situation after endogenous insulin secretion.² Continuous intraperitoneal insulin infusion (CIPII) has been available for more than 30 years but has only been used in very few patients around the world. With CIPII, insulin is directly infused into the intraperitoneal space where it is absorbed via the capillaries of the visceral peritoneum into the portal vein.^{3,4} Because it is absorbed directly into the portal system, there is a more physiological insulin distribution with a high hepatic uptake and relatively low peripheral plasma insulin concentrations compared with SC insulin injections and CSII.⁵ Intraperitoneal-administered insulin takes approximately 15 min to reach its peak effect and allows blood glucose values to return to the baseline level more rapidly, producing more physiological insulin profiles compared with SC insulin injections.⁶ Other possible positive effects include improvement of the impaired glucagon secretion and enhanced hepatic glucose production in response to hypoglycaemia.⁴ In this issue Van Dijk et al. present a prospective observational case-control study in type 1 diabetes patients

in which they compared glycaemic control and quality of life during long-term CIPII therapy with a control group treated with SC insulin therapy.⁷ They observed that glycaemic control during CIPII therapy was non-inferior to SC insulin therapy. In addition, the perceived health status among patients treated with CIPII was stable, but was poor compared with the patients treated with SC insulin.⁷ Therefore, Van Dijk et al. concluded that at present the costs of CIPII outweigh the advantages of CIPII for the majority of patients and they advocated CIPII only as a last-resort treatment for selected patients with type 1 diabetes.⁷ As the authors frankly admitted in the Discussion section of their paper, the non-randomised observational design is an important limitation of their study. In addition, at baseline the CIPII-treated patients in the study by Van Dijk et al., although matched for age and sex, had developed significantly more diabetic microvascular complications and had a longer duration of diabetes (29 vs. 26 years) than the SC control group.⁷ This could – at least partly – explain the lower perceived health status in the CIPII-treated patients compared with the SC insulin group.

CIPII is usually started late in the course of diabetes in highly selected populations with often a rather complex background and disease history. Most of these patients have 'brittle diabetes', i.e. failure to reach adequate glycaemic control despite intensive insulin therapy with multiple daily injections (MDI) or CSII and/or having frequent hypoglycaemic episodes. This was also the case for the patients included in the study by Van Dijk et al.⁷ In spite of inclusion of highly selected populations in most studies, a systematic review of the literature showed that CIPII is effective in type 1 diabetes in lowering and maintaining HbA1c levels, with strong evidence from randomised studies but low evidence from observational studies.⁸ Shisko et al. demonstrated that the route of insulin delivery plays an important role in glycaemic control.⁹ They compared the effects of CIPII (via the umbilical vein)

with insulin administered as CSII and with 'standard' intermittent SC therapy in 36 newly diagnosed young type 1 diabetes (i.e. diabetes duration of 1-3 weeks).⁹ Six months after the start of treatment, glycaemic control was almost normal in the patients in the CII group compared with those in the CSII group (HbA_{1c}: 5.3% vs. 7.9%).⁹ In addition, glycaemic excursions and the frequency of hypoglycaemia was significantly less during CII than with CSII. Moreover, CII was more effective than CSII in elevating total insulin-like growth factor-I (IGF-I) levels and decreasing IGF-binding protein-1 (IGFBP-1) levels and growth hormone (GH) secretion than CSII while it has recently been reported that the IGF-I bioactivity, which is more sensitive for monitoring the effects of therapeutic interventions than total IGF-I, was higher (i.e. more normal) in patients treated with CII compared with CSII.^{9,10} This shows that the route of insulin administration also plays an important role in the normalisation of the GH-IGF-I axis in type 1 diabetes. It has been further hypothesised that the low circulating IGF-I bioactivity in type 1 diabetes usually observed during SC insulin therapy results in chronically insufficient protective effects by IGF-I in the kidneys, eyes and neurons, and thus the progression of diabetic microvascular complications with ageing.¹¹ Therefore, intraperitoneal insulin administration may not only be beneficial by improving glucose control but also by correcting the alterations in the IGF system in type 1 diabetes.¹²

In their paper, Van Dijk et al. concluded that for the majority of patients the actual costs of CII in the management of type 1 diabetes seem, at the moment, to outweigh the advantages of CII. They advocated the use of CII only as a last-resort treatment option for highly selected patients with type 1 diabetes, who have been unable to reach the current treatment goals with current SC insulin therapy.⁷ However, many years of poor metabolic control of type 1 diabetes – as was already present at baseline in the diabetic patients included in the study by Van Dijk et al. – may have induced long-lasting harmful effects. These effects will not be arrested promptly and/or recovered completely after the start of CII. From epidemiological studies, it has become clear that after many years of poor metabolic control, there is less opportunity to positively influence the development and progression of diabetic complications in type 1 diabetes. On the contrary, based on the long-term results of the DCCT-Epidemiology of Diabetes Interventions and Complications (EDIC) study, the concept of glycaemic legacy has been proposed: strict glycaemic control in the very early phase of type 1 diabetes generates a legacy effect that may confer protection against or a delay in the long-term diabetic complications.^{13,14} By mimicking more normal physiological insulin secretion

than current therapies, CII is in my opinion still a promising treatment option for type 1 diabetes that once again deserves clinical attention. However, until now, the long-term effects of CII treatment when initiated at the very start of type 1 diabetes have never been studied. Therefore, new well-designed studies should be initiated to determine whether CII treatment started early in the course of diabetes can decrease morbidity and improve quality of life and in the long-term – compared with current treatment options – is superior in reducing diabetes complications.

DISCLOSURES

None.

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