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Diabetes & Metabolism 37 (2011) S40-S47

External insulin pump treatment in the day-to-day management of diabetes: benefits and future prospectives

H. Hanaire

Service de Diabétologie, Maladies Métaboliques et Nutrition, pôle cardiovasculaire et métabolique, CHU de Toulouse, Université de Toulouse, Toulouse, France

Abstract

The aim of diabetes treatment is to achieve tight glucose control to avoid the development of chronic diabetes complications while reducing the frequency of hypoglycaemic episodes. The main clinical indications of pump therapy in type 1 diabetes are persistently elevated HbA_{1c} in spite of the best attempts of intensified insulin therapy with multiple daily injections (MDI) and/or frequent, disabling or severe hypoglycaemia. Several trials have demonstrated the superiority of continuous subcutaneous insulin infusion (CSII) over MDI, and highlighted the benefits of using short-acting insulin analogues. However, new MDI regimens with long-acting insulin analogues challenge insulin pump therapy in some indications, thus indicating the need for precise selection of those patients who will benefit the most from CSII. In type 2 diabetes, pump therapy may be an invaluable tool in selected patients characterized by chronic elevation of HbA_{1c}, obesity and high insulin requirements. In addition, in any case, specific education, training and ongoing evaluation of the benefit/risk ratio of the treatment are mandatory. Furthermore, there is continuing progress in the development of pump and catheter features, and insulin kinetics can still be improved. These technical advances are part of the work in progress towards developing closed-loop systems.
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Keywords: *External insulin pump; Intensive insulin therapy; HbA_{1c}; Glycaemic control; Diabetes; Review*

Résumé

Intérêts et perspectives du traitement par pompe à insuline externe dans la prise en charge du diabète

Le but du traitement du diabète est d'obtenir un équilibre glycémique satisfaisant afin d'éviter le développement des complications chroniques du diabète et de réduire dans le même temps la fréquence des hypoglycémies. Les principales indications du traitement par pompe dans le diabète de type 1 sont l'augmentation durable de l'HbA_{1c} malgré un traitement intensif bien conduit par injections multiples, et la survenue d'hypoglycémies fréquentes, handicapantes, ou sévères. Plusieurs études ont démontré la supériorité du traitement par pompe par rapport aux injections multiples, et souligné les bénéfices apportés par l'utilisation des analogues de l'insuline rapide. Les nouveaux schémas qui utilisent les analogues longs de l'insuline entrent en compétition avec le traitement par pompe dans certaines indications, soulignant la nécessité d'une sélection précise des patients qui seront les plus grands bénéficiaires du traitement par pompe. Dans le diabète de type 2, le traitement par pompe peut être un outil intéressant chez des patients sélectionnés, caractérisés par un déséquilibre glycémique chronique, une obésité sévère et des besoins en insuline élevés. Dans tous les cas, une éducation spécifique, un entraînement à l'utilisation et une évaluation continue du rapport bénéfice/risque du traitement sont indispensables. Les caractéristiques des pompes et des cathéters sont en évolution permanente, la cinétique des insulines peut être encore améliorée. Ces avancées techniques font partie intégrante des travaux en cours pour le développement de systèmes en boucle fermée.
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Mots-clés : Pompe à insuline externe ; Insulinothérapie intensive ; HbA_{1c} ; Contrôle glycémique ; Diabète ; Revue générale

1. Introduction

The goal of type 1 diabetes treatment is to achieve tight glucose control to avoid chronic diabetes complications while limiting the frequency of hypoglycaemic episodes in day-to-day life. Over the past few decades, considerable efforts have been made to improve the tools of treatment. The development of continuous subcutaneous insulin infusion (CSII) and, more recently, short-acting insulin analogues with advantageous pharmacokinetic properties constitute important advances in the treatment of diabetes.

Correspondence.
E-mail: **hanaire.h@chu-toulouse.fr (H. Hanaire).**

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CSII using external insulin pumps was first introduced in the 1970s as a way of achieving and maintaining strict control of blood glucose concentrations in type 1 diabetes patients [1] through more physiological insulinization than achieved with multiple daily injections (MDI). The exclusive use of soluble short-acting insulin, infused subcutaneously at the same site for 2 or 3 days, reduces the variability of insulin absorption compared with long-acting insulins. CSII also allows greater flexibility of insulin infusion, thanks to the ability to program several basal rates and to adjust meal-time boluses when required. It is noteworthy that the modern intensified insulin regimens, whether delivered by CSII or MDI, all require the implementation of frequent blood glucose self-monitoring, dietary advice and structured diabetes education to improve glycaemic control. Under these conditions, CSII has proved superior to MDI in terms of HbA_{1c}, hypoglycaemic episodes, glucose variability and quality of life in those selected patients who fail to obtain good glycaemic control in spite of an intensified MDI regimen. These findings have also led to the validation by the French Health Authority of insulin pump treatment in patients who fail to obtain good glycaemic control with MDI [2], and to the recent publication of French recommendations for the use of CSII in type 1 and type 2 diabetes patients [3].

2. Benefits of CSII in type 1 diabetes

2.1. HbA_{1c}

Several studies have confirmed the superiority of CSII over MDI in terms of HbA_{1c} [4-7]. In the Diabetes Control and Complications Trial (DCCT) [8], HbA_{1c} levels in the intensive-treatment group were significantly lower with CSII than with MDI (ranging from -0.2% to -0.4%). However, because the patients who were randomly assigned to receive intensive treatment in the DCCT could choose between CSII and MDI (they were not randomly allocated to the type of intensive therapy), the results could be biased. Nevertheless, two recent meta-analyses of trials have compared CSII and MDI regimens, involving 600 and 1547 patients, respectively [9,10], and have reported an overall benefit of CSII over MDI, with a reduction of HbA_{1c} in the range of 0.4-0.5% that was associated with a reduction in insulin requirements. A recent Cochrane review reported a lower mean difference of 0.3% [11], but included studies of very short duration and early trials from the 1980s, when pumps were less reliable and less technically sophisticated.

As all of the trials included in these meta-analyses were performed with human regular insulin, except one study that used insulin lispro [12], it was necessary to investigate whether the introduction of short-acting insulin analogues would modify the relative performances of CSII and MDI. In fact, with either CSII or MDI, the optimal meal-time insulin is a short-acting insulin analogue, as this exhibits pharmacodynamic advantages over human regular insulin, including faster absorption, earlier onset and shorter duration of action.

Several randomized controlled trials have shown that CSII with short-acting insulin analogues is more efficient for postprandial glycaemia and HbA_{1c} concentrations than CSII with human regular insulin [13-15] (Table 1). A meta-analysis also concluded that the use of insulin analogues in pump therapy results in a modest (0.26%), but significant, reduction in HbA_{1c} compared with soluble insulin [16]. The pharmacokinetic properties of short-acting insulin analogues are certainly responsible for this slight superiority, thanks to improvements in postprandial glucose levels and stability.

However, the efficacy of CSII *vs* MDI therapy has been evaluated in only a limited number of randomized controlled trials in which rapid-acting analogues were used for both regimens, with two out of three concluding the superiority of CSII [14,17,18] (Table 2). A pooled analysis of the three studies suggested that CSII is associated with better glycaemic control, particularly in patients with initially suboptimal control [19]. The magnitude of the effect of CSII compared with MDI on glycaemic control was similar to the previous findings of trials using human regular insulin, with the difference in HbA_{1c} concentrations between CSII and MDI being -0.35%. Also, the relative benefit of CSII over MDI was found to increase with higher baseline HbA_{1c} levels (Fig. 1) [20]. In addition,

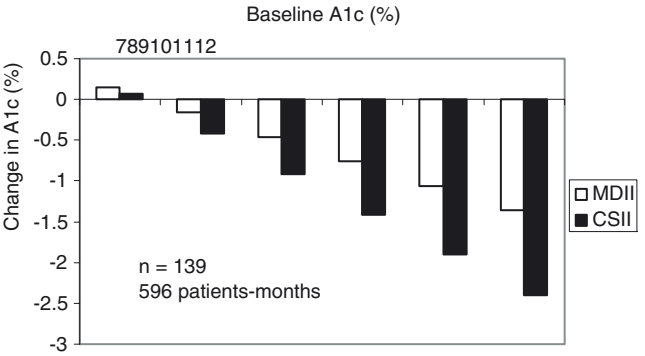

Fig 1. Predicted relative benefits of CSII over MDI in lowering HbA_{1c} according to baseline HbA_{1c} (adapted from [20]).

Table 1
Superiority of short-acting insulin analogues over human insulin in continuous subcutaneous insulin infusion (CSII) treatments.

Authors [reference]	Study design	Patients (n) and type of insulin	Difference in HbA_{1c}
Zinman et al., 1997 [13]	Double-blind crossover	30 CSII with lispro/Humulin	-0.34%
Melki et al., 1998 [14]	Open crossover	39 CSII with lispro/Actrapid	-0.53%
Renner et al., 1999 [15]	Open crossover	113 CSII with lispro/Humulin	-0.13%

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