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Position statement

Implantable insulin pumps. A position statement about their clinical use

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Abstract

Aim. – To review clinical use of implantable insulin pumps and to suggest indications for this therapy.

Methods. – The EVADIAC group performed a review of published reports on implantable insulin pumps for the last 15 years and analyzed its own centralized database. From this update, a position statement on indications of this therapy is drawn.

Results. – Published papers mostly report safety and effectiveness data from observational cumulated experiences of 15–350 patient-years. While HbA_{1c} reduction does not reach statistical significance in all reported studies, improvement of blood glucose stability and reduction of severe hypoglycaemia appear as constant characteristics of this therapy. When compared to subcutaneous insulin therapy in randomized controlled studies, implantable pumps allow significantly reduced blood glucose fluctuations and improved quality of life in both type 1 and type 2 diabetic patients, and a significant weight decrease in type 2 diabetic patients. While the EVADIAC registry shows the reduced occurrence of pump-pocket complications thanks to preventive measures and a lower incidence of catheter obstructions following improvements of catheter design, underdelivery due to insulin aggregation in pumps remains a recurrent although reversible issue. Determinants of increased anti-insulin antibody production in some patients remain elusive but impact on blood glucose control is limited in most cases.

Conclusion. – From analyzed data, the EVADIAC group states that implantable pumps can be safely indicated and provide metabolic improvements in type 1 diabetic patients who remain far from targeted HbA_{1c} below 7% and/or experience large fluctuations of blood glucose including recurrent severe hypoglycaemia, in spite of intensive follow-up and education when treated by subcutaneous insulin.

Résumé

Pompes à insuline implantables : prise de position sur leur utilisation clinique.

But. – Faire une revue sur l'utilisation clinique des pompes à insuline implantables, et proposer des indications pour ce traitement.

Méthodes. – Le groupe EVADIAC a réalisé une revue des données publiées sur les pompes à insuline implantables au cours des 15 dernières années et a analysé sa propre base de données centralisée. À partir de cette mise à jour, une position sur les indications de ce traitement est prise.

Résultats. – Les publications rapportent pour la plupart des données de sécurité et d'efficacité issues d'expériences observationnelles cumulées de 15 à 350 années-patients. Tandis que la réduction de l'HbA_{1c} n'atteint pas la significativité statistique dans tous les rapports, une amélioration de la stabilité glycémique et une réduction des hypoglycémies sévères apparaissent comme des caractéristiques constantes de ce traitement. Quand elles sont comparées à l'insulinothérapie sous-cutanée dans des études randomisées contrôlées, les pompes implantables permettent de réduire de façon significative les fluctuations glycémiques et d'améliorer la qualité de vie chez les diabétiques de type 1 et de type 2, et une baisse significative du poids chez les sujets diabétiques de type 2. Alors que le registre d'EVADIAC montre la survenue réduite des complications de poches de pompe grâce des mesures préventives et une incidence plus faible des obstructions de cathéter après l'amélioration de la conformation du cathéter, le défaut de perfusion dû à l'agrégation d'insuline dans les pompes reste un problème récurrent bien que réversible.

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Les déterminants de la production accrue d'anticorps anti-insuline chez certains patients demeurent mal identifiés mais l'impact sur le contrôle glycémique est limité dans la plupart des cas.

Conclusion. – D'après les données analysées, le groupe EVADIAC énonce que les pompes implantables peuvent être indiquées avec sécurité et procurer des améliorations métaboliques chez les diabétiques de type 1 qui restent loin de l'HbA_{1c} cible de 7 % et/ou présentent de grandes fluctuations glycémiques incluant des hypoglycémies sévères récurrentes, malgré un suivi et une éducation intensifiés sous traitement par insuline sous-cutanée.

Keywords: Implantable devices; Intraperitoneal insulin delivery; Intensive insulin therapy; Type 1 diabetes mellitus; Review

Mots clés : Dispositifs implantables ; Perfusion d'insuline intrapéritonéale ; Traitement intensif par l'insuline ; Diabète de type 1 ; Revue générale

1. Introduction

A current challenge when treating type 1 diabetic patients is to reach sustained near-normoglycaemia to prevent long-term complications with no significant increase in the incidence of hypoglycaemia. The intensively treated patients involved in the Diabetes Control and Complications Trial (DCCT) well exemplified this problem since they maintained an HbA_{1c} level almost 2% lower than the control patients while they experienced a three times higher incidence of severe hypoglycaemia [1]. Besides, the lack of significant difference of measured quality of life between the two treatment groups [2], in spite of a more than 50% decrease in diabetic complications in the intensive treatment arm, raised the question of the feasibility and the acceptability in common practice of aiming at near-normoglycaemia by the use of multiple daily subcutaneous insulin injections or continuous subcutaneous insulin infusion (CSII). The follow-up of the DCCT, namely EDIC, well demonstrated how near-normoglycaemia could not be maintained using these therapeutic tools when intensive coaching vanished [3].

Initiated before the DCCT, education strategies focusing on patient empowerment in the management of similar modalities of subcutaneous insulin therapy showed that this inverse relationship between the decrease of HbA_{1c} and the increase of severe hypoglycaemia is not unavoidable [4–6]. Thus, significant improvements of blood glucose control have been reported without significant increases in the occurrence of severe hypoglycaemic events [5,6]. However, patient knowledge and skills in the optimized use of subcutaneous insulin therapy appear to need iterative training sessions to keep the efficacy on blood glucose control, as shown by the follow-up of the DAFNE study [6]. Post-DCCT availability of insulin analogues, which allow more physiological insulin kinetics and a better reproducibility of insulin action, also resulted in a lower incidence of hypoglycaemia at similar or lower HbA_{1c} levels when compared to the use of regular and NPH insulin [7–10].

The choice of an alternative route of insulin delivery in order to by-pass the obstacles related to the limited reproducibility of insulin action associated with subcutaneous injections or infusion has motivated the development of implantable insulin pumps [11]. Besides, the goal of freeing patients from needles and external devices for diabetes treatment also supported the move toward implantable infusion devices. After initial attempts to use the IV route that resulted in complications at infusion site [12], and following the choice of pulsatile rather than peristaltic infusion to minimize mechanical trauma to insulin solutions [13], the peritoneal route has been selected as the most adequate for insulin infusion from implantable pumps.

Implantable pump experience using these pulsatile infusion devices started in the late 80s and early 90s with the systems from three pump manufacturers: Infusaid Inc. (Norwood, MA, USA), MiniMed (Sylmar, CA, USA) and Siemens-Elema (Solna, Sweden) [12,14,15]. Whereas Siemens-Elema and Infusaid Inc. stopped their manufacturing activity in the mid-90s, MiniMed that merged with Medtronic (Northridge, CA, USA) from 2002 still maintained implantable insulin pump production until nowadays. A specific insulin preparation, HOE 21PH has been elaborated by Hoechst (Frankfurt, Germany) in the early 80s to be used in implantable devices [16]. Because of the physical conditions to which insulin is submitted in these devices, a stabilizing agent, genapol, has been added in the solution to prevent aggregation. Whereas implantable insulin pump models 2001 and 2007 (Fig. 1) from MiniMed have been approved for clinical use in European Union, HOE 21PH insulin has remained an investigational product until now. These legal conditions have limited the expansion of the clinical use of implantable insulin pumps. Recent approval of HOE 21PH insulin, under the name Insuplant®, for clinical use should allow a wider development of implantable insulin pump therapy in the European Union in forthcoming years.

In this paper, the EVADIAC group reviews reported data on the experience of implantable pump therapy for these last 15 years in order to update its previously reported statement on the clinical use of implantable insulin pumps [17] and to suggest current indications for this therapy.

2. Methods

In order to prepare the present position statement, the EVADIAC group members identified by a Medline search the list of papers that have been published on implantable insulin pump therapy from 1990 to present time. Besides, EVADIAC central registry of data gathered on this therapy for the same period has been examined. Each EVADIAC center was responsible for the specific review of one or two topics dealing with