

Position statement

Implantable insulin pumps. A position statement about their clinical use

E. Renard*, P. Schaepelynck-Bélicar, on behalf of the EVADIAC group¹

Service des maladies endocriniennes, hôpital Lapeyronie, 34295 Montpellier cedex 05, France

Received 22 June 2005; accepted 6 October 2006

Available online 14 February 2007

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.

© 2007 Elsevier Masson SAS. All rights reserved.

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.

* Corresponding author.

E-mail address: e-renard@chu-montpellier.fr (E. Renard).

¹ EVADIAC Group: B. Catargi, H. Gin (hôpital du Haut-Lévêque, Bordeaux), J.-P. Riveline, G. Charpentier (hôpital Gilles-de-Corbeil, Corbeil), S. Rudoni, J.-M. Brun (hôpital du Bocage, Dijon), J.-F. Martin (centre hospitalier, Le Mans), C. Fermon, P. Fontaine (clinique Marc-Linquette, Lille), B. Mestre (centre hospitalier Lyon-Sud, Lyon), P. Schaepelynck-Bélicar, L. Rocher, L. Dufaitre, V. Lassmann-Vague (hôpital Sainte-Marguerite, Marseille), E. Renard, J. Bringer, D. Apostol (hôpital Lapeyronie, Montpellier), N. Laguerre-Lang, B. Guerci (hôpital Jeanne-d'Arc, CHU de Nancy, Toul), A. Sola-Gazagnes, M.-J. Haardt, J.-L. Selam, G. Slama (Hôtel-Dieu, Paris), C. Leborgne, H. Grulet (centre hospitalier universitaire, Reims), A.-M. Leguerrier, D. Maugendre†, I. Guilhem (centre hospitalier universitaire, Rennes), B. Estour, L. Millot, M. Kadem (hôpital Bellevue, Saint-Etienne), L. Meyer, N. Jeandidier, M. Pinget (centre hospitalier universitaire, Strasbourg), V. Melki, H. Hanaire (hôpital Rangueil, Toulouse).

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.

© 2007 Elsevier Masson SAS. All rights reserved.

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

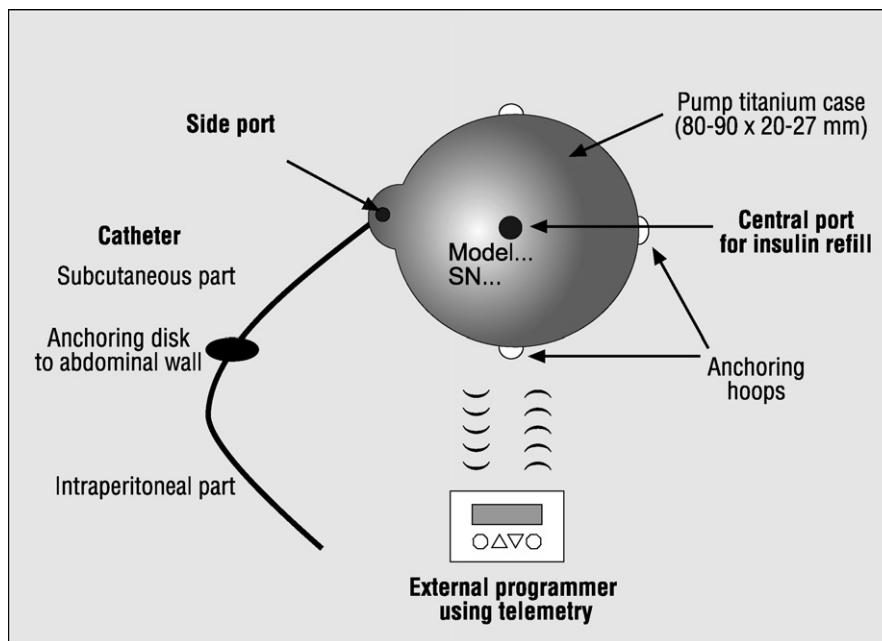


Fig. 1. Scheme of an implantable insulin pump.

implantable insulin pumps, e.g. efficacy studies, underdelivery issues, etc.

All cumulated information from this dual process has been shared among EVADIAC members at two specific 1-day internal meetings during which each reviewed topic was presented by the responsible center and discussed with the other centers until a consensus view could be established. P. S.-B. and E.R. were nominated to write this position statement on behalf of EVADIAC group.

3. Results

3.1. Safety of implantable pump therapy

Safety issues when using implantable insulin pumps, although showing a decreased incidence during the most recent period [18,19], are dominated by complications at the abdominal implantation site ('pump-pocket') and insulin underdelivery episodes. Other issues also deserve considerations, such as anti-insulin antibody variations and peritoneal reactions that were recently reported in subjects undergoing recurrent catheter obstructions.

3.1.1. Pump-pocket complications

Reported occurrence of pump-pocket complications decreased from 8 to less than 2 per 100 patient-years from the early 90s to the current period [19–22]. Large inter-center discrepancies in the frequency of pump-pocket complications have been identified inside the EVADIAC group. From reviewed literature and case analysis from the EVADIAC registry, complications at implantation site appeared to be of two main different types.

So-called mechanical complications are characterized by a fluid accumulation in the pump-pocket and/or a skin thickening

at the pump implantation site that predominates in front of pump peripheral edges. Fluid drainage by needle-puncture reveals a clear yellowish liquid free of bacteria and neutrophils. These incidents mainly occur during the first weeks or months after implantation and resolve by rest and wearing of an abdominal compression belt. These events can be effectively prevented by leaving the patient at bed rest for 24–48 hours following the implantation and by wearing an abdominal compression belt for the first 4–6 post-operative weeks while limited physical exercise is recommended. Future reductions of pump size and thickness are expected to further minimize these events.

However, most problems occurring at implantation site are related to an infection [22,23]. They generally develop as a progressive and persistent fluid accumulation in the pump-pocket, associated with an initial or gradually increasing inflammatory local skin reaction, which may ultimately lead to erosion. Identified germs are mostly coagulase-negative staphylococci or propionibacterium acnes, suggesting a bacterial seeding from skin flora [23]. Surgical interventions for implantation or catheter replacement as well as iterative transcutaneous punctures of the pump-pocket for insulin refills and investigation procedures on the implanted system in case of underdelivery are considered as likely responsible for bacterial seeding. Because these infectious complications result in pump explantation in all cases, prevention measures appear as crucial. During these last years, specific procedures have been followed by the EVADIAC centers, almost allowing a suppression of these adverse events (EVADIAC Registry, unpublished data). They include:

- careful pre-surgical preparation of future implantation site: exclusion of any insertion of subcutaneous insulin infusion catheter during 4–6 weeks before pump implantation, thor-

ough skin examination the day before surgery in order to post-pone implantation if needed, non traumatic shaving, antiseptic cleaning of abdominal skin with iodated povidone or hexamidin in the previous evening and in the morning before surgery. Although infectious seeding of hematogenous origin is very uncommon, preliminary screening and eradication of any urinary, digestive, pulmonary, and dental or upper respiratory tract silent infection site is also commonly performed before implantation;

- forty-eight-hour IV antibiotic coverage of implantation and eventual re-interventions on the pump-pocket, using either cefazolin or vancomycin (in case of allergy to beta-lactams) and starting within the half-hour preceding skin incision;
- strict respect of aseptic rules by a trained personnel during each transcutaneous access to the pump-pocket. Systematic antiseptic cleaning of skin using iodated povidone or hexamidin is performed before each procedure on the implanted system. The vigilance is extended to the ventilation system and to the cleaning conditions of the facility. Systematic antibiotic coverage is performed for outpatient procedures that last more than 15 min and include repeated or sustained puncture of the pump-pocket. Only a few EVADIAC centers extend it to routine pump refills.

In order to prevent any recurrence of infection on the replacement system when an explantation has been motivated by a pump-pocket infection, a 3-month delay after the end of the antibiotic treatment is requested before surgical replacement. The opposite low abdominal quadrant is preferred for the next implantation.

3.1.2. Underdelivery problems

Insulin underdelivery represents the most usual event that occurs with implantable pump therapy. Cases requiring surgical re-intervention, for catheter replacement or laparoscopic cleaning, decreased during the last decade, from 13 to less than 4 per 100 patient-years [19,24]. Meanwhile, the occurrence of cases related to the formation of insulin aggregates in the pumping mechanism still ranged from 30 to 40 for 100 patient-years [19]. These latter incidents, that have been related to a lack of physical stability of insulin preparations when in contact with pump materials [25–27], are reversible in most cases by using an outpatient procedure of pump rinsing using sodium hydroxide (0.1 N NaOH).

Insulin underdelivery is most often disclosed by a gradual increase of the percent default of insulin infusion ('error percentage'), measured at each pump refill. A threshold of 15% underdelivery is considered as meaningful [25]. An impairment of blood glucose control is commonly associated, that may be controlled by a proportional increase of programmed insulin doses by the patient [25]. Taking into account that insulin aggregation in the pumping mechanism is the most usual cause for underdelivery, a pragmatic attitude is commonly followed that includes a rinsing of the pump with 0.1 N NaOH for 10 min to get rid of aggregates, associated with a flushing of

the catheter via the side port to remove any possible combined partial obstruction. The failure of this procedure to restore normal insulin delivery requests further investigation aiming at the disclosure of a catheter obstruction [28]. An X-ray examination of the catheter after contrast medium injection through the side port usually leads to the diagnosis of catheter tip obstruction or encapsulation by a peritoneal membrane. Recent trials suggest CT scan after contrast medium injection in the catheter as a more accurate procedure to identify encapsulations in doubtful cases [29]. Catheter obstructions can only be cured by catheter replacement or laparoscopic cleaning of catheter tip [28].

Insulin underdelivery may also occur, although much less frequently, as an acute event, resulting in a sudden hyperglycaemia prone to ketosis, which can only be controlled by SC insulin. Three possible causes may be responsible for this acute failure of the implanted system: 1) a pump stop due to an electronic failure, 2) an extended insulin precipitation in the pumping mechanism that results in pump blockage, 3) a complete acute obstruction of the catheter (EVADIAC Registry, unpublished data).

Pump stop is uncommon but easily diagnosed by a specific alarm on the programmer screen. After device explantation for further analysis by the manufacturer, only pump replacement can restore intra-peritoneal (IP) insulin therapy. Extended insulin aggregation in the pumping mechanism is detected by the disclosure of a lack of pump strokes when a derivation line is connected through the side port at the pump outlet. Catheter obstruction results in the failure of a flushing procedure through the side port whereas pump strokes look normal. Pump blockage by massive insulin aggregation may sometimes be rescued by a prolonged pump rinsing for several hours using NaOH, otherwise requests pump replacement. Catheter obstruction is commonly solved by catheter replacement.

3.1.3. Anti-insulin antibody variations

Several studies reported in the 90s an increase of anti-insulin antibody plasma levels during IP insulin infusion from implantable pumps [30–32]. Antibody levels significantly increase as soon as the third month following implantation and then most often plateau throughout the treatment duration. Of note, this immune reaction is very variable among patients since ranging from null to massive. Currently, the only identified predictive factor appear to be initial anti-insulin antibody level before implantation: increment of antibodies is tightly related to pre-existing antibody levels [30,31].

Several immunogenic factors may be considered to understand this phenomenon: HOE 21 PH insulin formulation itself, although its SC infusion does not increase antibody levels, peritoneal route since the peritoneum is a macrophage-rich area, that may promote lymphocyte activation and antibody production, insulin aggregates formed in the pumping mechanism which have been shown as strongly immunogenic [33,34].

In most patients, anti-insulin antibody increase has only few outcomes on blood glucose control, such as reduced plasma free insulin peaks after bolus that may result in impaired post-meal control [35]. No clear relationship can be established

between these blood glucose excursions and plasma antibody levels. The ‘low morning syndrome’ looks as a close phenomenon, with larger amplitude [30,31]. In such cases, post-meal hyperglycaemic swings despite high increase of bolus doses are combined with extended hypoglycaemia during the second half of the night despite a minimal basal rate of insulin delivery. The role of low affinity anti-insulin antibodies, which are better identified by ELISA assays than by RIA assays, acting as a circulating ‘reservoir of insulin’, has been suggested to explain these observations [31]. In some cases of ‘low morning syndrome’, 10–20 mg hydrocortisone at bedtime has been able to reduce the occurrence and the severity of nocturnal hypoglycaemia. Of note, when IP insulin delivery has been interrupted, this syndrome usually improved within 3 months (EVADIAC Registry, unpublished data).

Only four patients included in EVADIAC registry showing high anti-insulin antibody levels have developed rapid severe insulin resistance. This phenomenon was solved by various treatments including interruption of IP insulin delivery, replaced by IV insulin infusion, temporary corticosteroids or IV infused immunoglobulins [36]. Simultaneous decrease of anti-insulin antibody levels suggests that insulin resistance was related to the binding of infused insulin to anti-insulin antibodies that inhibited insulin action.

This immune response against insulin does not extend to a more generalized autoimmune reaction, as it has been clearly shown by a recent EVADIAC prospective study [37]. However, two reported cases of aseptic peritonitis revealed by recurrent catheter encapsulations might also be related to an immune reaction against insulin [38].

3.2. Effectiveness of implantable insulin pumps

3.2.1. Pharmacokinetics

IP insulin delivery has been characterized as a mean to allow faster insulin absorption and action versus SC route as well as sooner return to baseline plasma insulin level after an insulin bolus [39–41]. Reproducibility of plasma insulin levels after bolus programming from an implanted pump has also been reported [42]. Besides, a positive portal/systemic plasma insulin ratio is restored when insulin is infused IP with lower basal peripheral plasma insulin levels [43]. A more rapid clearance of insulin after IP versus SC insulin delivery has been suggested as the reason why severe hypoglycaemia occurs

less frequently with implantable pumps [44]. Lower basal insulin levels when using IP route may also contribute to the restoration of glucagon secretion at exercise and after hypoglycaemia when using prolonged IP infusion [45,46].

3.2.2. Observational studies

Table 1 reports blood glucose improvements that have been observed in observational studies assessing the feasibility of implantable pump therapy, where patients were moved from SC to IP insulin delivery [12,14,24,47]. HbA_{1c} levels did not decrease significantly in all studies, but standard deviation (S.D.) of blood glucose levels appeared constantly reduced when assessed [14,24]. Besides, EVADIAC data have shown the dramatic reduction of severe hypoglycaemic events while using IP insulin [15]. Further more, recurrence of severe hypoglycaemia has been reported when moving back to SC route [48]. A more recent comparative short-term study was performed by the EVADIAC group in fourteen type 1 diabetic patients who moved from CSII using lispro insulin to implantable pumps [49]. Reported data show that IP insulin treatment led to significantly lower blood glucose levels, noticeably pre-meal values. HbA_{1c} and blood glucose stability were also significantly improved by implantable pumps. Dutch investigators also recently reported their experience about implantable insulin pumps in patients with brittle diabetes [50]. Investigated patients showed poor metabolic control and related frequent hospital admissions when recruited. Although achieved metabolic control with implantable pumps on long-term was still far from near-normoglycaemia, a significant sustained reduction of HbA_{1c} was obtained and average yearly hospital stay was dramatically reduced from 45 to 13 days ($P = 0.005$).

3.2.3. Randomized controlled studies

Randomized studies that compared IP vs. SC insulin delivery have been limited. A first one in type 1 diabetic patients compared multiple daily insulin (MDI) injections or continuous subcutaneous insulin delivery (CSII) vs. insulin delivery from implanted pumps for 6 months, after a 3 month-optimization with MDI or CSII [51]. While HbA_{1c} levels were similarly reduced with both treatments, blood glucose values over 11 mmol/l as well as S.D. of blood glucose values were significantly reduced during IP use. A second one, performed to assess cost-effectiveness of CSII vs. implantable pump therapy, using a cross-over design, reported lower HbA_{1c} levels with IP

Table 1
Effectiveness of implantable insulin pumps for the treatment of type 1 diabetes mellitus during feasibility studies

Authors (pump model, manufacturer)	References	Cumulated experience (patient-years)	HbA _{1c} (%)		Severe Hypoglycaemias (n/p-y)	S.D. of blood glucose (mM/l)	
			Initial	Final		Initial	Final
Point Study Group (Promedos ID 1, Siemens AG)	[47]	18.2	7.6 (5.9–9.1)	7.0 (5.7–8.3) ($p < 0.05$)	0.22	NA	NA
Saudek et al. (PIMS, MiniMed Inc.)	[14]	28	9.2 ± 0.4	8.2 ± 0.4	0.00	NP	NP ($p < 0.01$)
Selam et al. (Model 1000, Infusaid)	[12]	73	7.4 ± 1.2	7.1 ± 1.0	0.05	NA	NA
Hanaire-Broutin for EVADIAC (MIP 2001, MiniMed Inc., Model 1000, Infusaid, Promedos ID 3, Siemens Elema)	[24]	353	7.4 ± 1.8	6.8 ± 1.0 ($p < 0.001$)	0.025		3.8 ± 0.8 ($p < 0.001$)

NA: values not available; NP: values not provided in article.

insulin delivery, reduced glycaemic fluctuations and fewer mild hypoglycaemic events after 6 months, all significantly [52]. However, direct costs, including pump acquisition, implantation, and follow-up, were 2.6-fold higher with IP than with SC delivery. The third one, performed in type 2 diabetic patients, in which IP and optimized SC insulin delivery were randomized and followed for 6 months in parallel groups, showed similar HbA_{1c} improvements but S.D. of blood glucose values and body weight were significantly lower with implanted pumps [53].

3.2.4. *Quality of life assessments*

Quality of life of patients treated by implantable pumps has been assessed by the Diabetes Quality of Life questionnaire used in DCCT trial in three studies. In an observational longitudinal study, patient satisfaction was significantly improved when moving from MDI or CSII to implantable pump therapy [12]. In the randomized study reported above in type 2 diabetic patients, impact of diabetes was rated significantly lower in patients treated by implanted pumps [53]. A more recent cross-sectional study reported better satisfaction in patients treated by implantable pumps than in patients using CSII or MDI [54].

4. Discussion

From this review of published papers on implantable insulin pump treatment for the last 15 years and the analysis of EVADIAC registry, the EVADIAC members reached a consensus on proposals for current indications and contra-indications of this therapy.

The first addressed question was: ‘When implantation of an insulin pump should be considered?’

EVADIAC members agree on three main clinical situations that should lead to the question of pump implantation. The first one is when intensive SC insulin treatment using CSII fails to control hyperglycaemia in spite of reinforced patient education and tight medical follow-up. Current recommended target for HbA_{1c} in type 1 diabetes mellitus is below 7%. Because of the increased risk of diabetic complications that is associated with this situation [1], IP insulin treatment using implantable pump should be considered.

The second clinical situation is when therapeutic target is reached at the cost of a low immediate benefit/risk ratio. Subjects reaching an HbA_{1c} level below 7% at the expense of recurrent severe hypoglycaemia or frequent mild hypoglycaemia raise the question of expected long-term benefit in terms of complications versus immediate risk of harmful outcomes of a severe hypoglycaemic episode and poor diabetes-related quality of life.

Third, the question of using an implantable pump may be raised by some patients as a mean to improve their diabetes-related quality of life. These patients complain mostly about the performance of multiple daily injections or the burden related to external carriage of pump and catheter.

The second addressed question was: ‘In which situations implantable pump therapy has been shown to provide a clear benefit?’

The first kind of situations includes cases where SC insulin treatment fails to reach glucose control because of defective or highly variable SC absorption of insulin. Such a clinical condition may be related to SC insulin resistance, poor tolerance and lack of effectiveness of SC insulin (e.g. Buschke’s non systemic scleroderma) or skin reactions to injections or at infusion sites when using CSII (e.g. lipodystrophies). In these situations, diffusion of insulin from skin is not reliable and results in chronic hyperglycaemia. Implantable insulin pump treatment, that bypasses SC barrier, has been shown as an effective therapy [55]. Of note, major subcutaneous insulin resistance, as described by Paulsen et al. [56], is a very rare phenomenon but represents a rational indication for IP insulin delivery. This diagnosis should be considered in front of a discrepancy between massive requirements of insulin when administered via SC route and normal requirements of insulin with IV route. There is no threshold value for establishing the diagnosis but a SC/IV dose ratio of 3/1 could be suggested. In EVADIAC experience, insulin doses have been dramatically reduced and blood glucose control considerably improved on long-term in four patients presenting this pattern [57]. Behavioral disorders (e.g. omission of SC injections or bolus programming) must however always be excluded in such situations and careful inpatient assessment is mandatory before concluding to SC insulin resistance.

High blood glucose variability with unpredictable hyper- and hypoglycaemic fluctuations, neither related to an irrelevant therapeutic behavior, nor secondary to apparent skin abnormalities, while using CSII is the second situation where the benefit of implantable pump therapy can be expected. The reduction of S.D. of blood glucose values has indeed been shown as a specific advantage of implantable pump use [14,24,49,58]. Some of these patients may either present recurrent severe hypoglycaemic episodes or very frequent non severe hypoglycaemia. Although arbitrary, the occurrence of at least two severe hypoglycaemic episodes per year and/or at least four episodes of mild hypoglycaemia per week could be considered as criteria that would lead to the question of an implantable pump because this therapy has been demonstrated as able to lower the incidence of hypoglycaemic episodes below these thresholds [15,58]. However, because they fear hypoglycaemia and/or because they present hypoglycaemia unawareness following recurrent hypoglycaemia, some of these patients may also present with chronic hyperglycaemia due to conservative behaviors about insulin doses, but with a previous history of frequent and/or severe hypoglycaemic episodes.

Another situation where implantable pumps have been shown as useful is represented by patients with sustained poor metabolic control due to their poor acceptance and management of insulin therapy, resulting in frequent hospital admissions. The Dutch experience reported above has shown relative benefits of implantable pump therapy in such difficult cases [50]. Of note, cost-effectiveness is in favor of implantable pump in this situation.

A third addressed question was: “Are there alternative therapies to implantable pumps when blood glucose control cannot be achieved with intensive SC insulin therapy?”

Also using IP insulin delivery, the DiaPort[®] experience has reported a significant reduction of severe hypoglycaemic episodes and improved quality of life in patients showing frequent blood glucose swings while using CSII [59]. Use of this device that allows IP insulin infusion from external pumps via a catheter implanted through a SC port is however associated with very frequent complications at implantation site and sometimes abdominal pain due to the stiffness of the catheter, both adverse events raising the question of possible long-term use.

From Edmonton experience, islet transplantation has become an acceptable and effective option for the therapy of patients with very frequent severe hypoglycaemic episodes [60]. Availability of islets remains however limited and immune suppression may induce significant adverse events [61]. Moreover, long-term effectiveness of islet transplantation is still under investigation and patients with nephropathy represent contra-indications for this therapy. Until further improvements in this therapy can be obtained, implantable pump therapy will keep the advantages of larger availability and more favorable long-term benefit/risk ratio.

The final addressed question was: “Which situations should be considered as contra-indications of implantable pump therapy?”

EVADIAC members agreed that patients who should not be considered for intensive insulin therapy would represent contra-indications of implantable pump in most cases.

This position would definitely be confirmed in following situations: severe psychological disturbances affecting skills in the management of insulin therapy, serious eating disorders that prevent any possible glucose control, ischemic retinopathy until achieved appropriate laser therapy to avoid impairment by rapid blood glucose lowering, associated severe co-morbidity affecting on short-term life expectancy or patient ability to manage insulin therapy.

Specific contra-indications are first related to the risk of malfunctions of the implanted system due to environmental conditions, such as exposure to magnetic fields of high intensity, very high temperatures, low atmospheric pressure (extended stays at an altitude higher or equal to 2500 m) or high atmospheric pressure (underwater diving exceeding 8.50 m).

Children or teenagers who have not yet reached adult size should not be considered as possible candidates for anatomic reasons, considering the current bulkiness of the implantable devices.

According to the regulations of clinical trials in Europe, pregnancy should not have been allowed in women treated by implanted pump until infused insulin had completed marketing approval. However, in EVADIAC experience, some patients became unexpectedly pregnant while treated by implanted pumps. None of these pregnancies had deleterious outcomes [62].

In all cases where the expected benefit of using implantable pump for diabetes therapy is unclear according to reported literature, the indication of pump implantation should result from an extended analysis of the individual clinical status, by an experienced staff, and should be elected after several physicians' consensus.

This position statement of EVADIAC group, based upon a cumulated 15-year experience with implantable insulin pumps, will hopefully constitute a framework for a safe and effective diffusion of this therapy. Through this statement and by sharing its clinical experience regarding the use of implantable pumps, the EVADIAC group wishes to promote what appears as a real step forward to improve diabetes treatment in difficult cases.

References

- [1] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–86.
- [2] The Diabetes Control and Complications Trial Research Group. Influence of intensive diabetes treatment on quality-of-life outcomes in the Diabetes Control and Complications Trial. *Diabetes Care* 1996;19:195–203.
- [3] The Writing Team for the Diabetes Control and Complications Trial–Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA* 2002;287:2563–9.
- [4] Muller UA, Femerling M, Reinauer KM, Risse A, Voss M, Jorgens V, et al. Intensified treatment and education of type 1 diabetes as clinical routine. A nationwide quality-circle experience in Germany (ASD). *Diabetes Care* 1999;22(Suppl 2):B29–B34.
- [5] Hunger-Dathe W, Braun A, Muller UA, Schiel R, Femerling M, Risse A. Insulin pump therapy in patients with type 1 diabetes mellitus: results of the Nationwide Quality Circle in Germany (ASD) 1999–2000. *Exp Clin Endocrinol Diabetes* 2003;111:428–34.
- [6] DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with Type 1 diabetes: dose adjustment for normal eating (DAFNE) randomized controlled trial. *Diabet Med* 2003;20(Suppl 3):4–5.
- [7] Lalli C, Ciofetta M, Del Sindaco P, Tolone E, Pampanelli S, Compagnucci P, et al. Long-term intensive treatment of type 1 diabetes with the short-acting insulin analog lispro in variable combination with NPH insulin at mealtime. *Diabetes Care* 1999;22:468–77.
- [8] Melki V, Renard E, Lassmann-Vague V, Boivin S, Guerci B, Hanair-Broutin H, et al. Improvement of HbA1c and blood glucose stability in IDDM patients treated with lispro insulin analog in external pumps. *Diabetes Care* 1998;21:977–82.
- [9] Vague P, Selam JL, Skeie S, De Leeuw I, Elte JW, Haahr H, et al. Insulin detemir is associated with more predictable glycaemic control and reduced risk of hypoglycaemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. *Diabetes Care* 2003;26:590–6.
- [10] Porcellati F, Rossetti P, Pampanelli S, Fanelli CG, Torlone E, Scionti L, et al. Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with type 1 diabetes mellitus given meal-time lispro insulin. *Diabet Med* 2004;21:1213–20.
- [11] Wredling R, Liu D, Lins PE, Adamson U. Variation of insulin absorption during subcutaneous and peritoneal infusion in insulin-dependent diabetic patients with unsatisfactory long-term glycaemic response to continuous subcutaneous insulin infusion. *Diabete Metab* 1991;17:456–9.
- [12] Selam JL, Micossi P, Dunn FL, Nathan DM. Clinical trial of programmable implantable insulin pumps for type 1 diabetes. *Diabetes Care* 1992;15:877–85.

- [13] Selam JL, Charles MA. Devices for insulin administration. *Diabetes Care* 1990;13:955–79.
- [14] Saudek CD, Selam JL, Pitt HA, Waxman K, Rubio M, Jeandidier N, et al. A preliminary trial of the programmable implantable medication system for insulin delivery. *N Engl J Med* 1989;321:574–9.
- [15] Broussolle C, Jeandidier N, Hanaire-BROUTIN H, for the Evadiac Study Group. French multicenter experience with implantable insulin pumps. *Lancet* 1994;343:514–5.
- [16] Grau U, Saudek CD. Stable insulin preparation for implanted insulin pumps. Laboratory and animal trials. *Diabetes* 1987;36:1453–9.
- [17] Lassmann-Vague V, Guerci B, Hanaire-BROUTIN H, Pinget M, Renard E, Selam JL, et al., on behalf of the EVADIAC group. Use of implantable insulin pumps: the EVADIAC position. *Diabetes Metab* 1997;23:242–50.
- [18] Gin H, Melki V, Guerci B, Catargi B, the EVADIAC Study Group. Clinical evaluation of a newly designed compliant side port catheter for an insulin implantable pump: the EVADIAC experience. *Diabetes Care* 2001;24:175.
- [19] Gin H, Renard E, Melki V, Boivin S, Schaepleynck-Belicar P, Guerci B, et al., the EVADIAC Study Group. Combined improvements in implantable pump technology and insulin stability allow safe and effective long term intraperitoneal insulin delivery in type 1 diabetic patients: the EVADIAC experience. *Diabetes Metab* 2003;29:602–7.
- [20] Renard E, Bringer J, Jacques-Apostol D, Lauton D, Mestre C, Costalat G, et al. Complications of the pump-pocket may represent a significant cause of incidents with implanted systems for intraperitoneal insulin delivery. *Diabetes Care* 1994;17:1064–6.
- [21] Scavini M, Cristallo M, Sarmiento M, Dunn FL, The infusaid multicenter Implantable insulin pump study group. Pump-pocket complications during long-term insulin delivery using an implanted programmable pump. *Diabetes Care* 1996;19:384–5.
- [22] Belicar P, Lassmann-Vague V, the EVADIAC Study Group. Local adverse events associated with long-term treatment by implantable insulin pumps. *Diabetes Care* 1998;21:325–6.
- [23] Renard E, Rostane T, Carriere C, Marchandin H, Jacques-Apostol D, Lauton D, et al. Implantable insulin pumps: infections most likely due to seeding from skin flora determine severe outcomes of pump-pocket seromas. *Diabetes Metab* 2001;27:62–5.
- [24] Hanaire-BROUTIN H, Broussolle C, Jeandidier N, Renard E, Guerci B, Haardt MJ, et al., the EVADIAC Study Group. Feasibility of intraperitoneal insulin therapy with programmable implantable pumps in IDDM: a multicenter study. *Diabetes Care* 1995;18:388–92.
- [25] Renard E, Bouteleau S, Jacques-Apostol D, Lauton D, Gibert-Boulet F, Costalat G, et al. Insulin underdelivery from implanted pumps using peritoneal route: determinant role of insulin-pump compatibility. *Diabetes Care* 1996;19:812–7.
- [26] Renard E, Souche C, Jacques-Apostol D, Lauton D, Gibert-Boulet F, Costalat G, et al. Improved stability of insulin delivery from implanted pumps using a new preparation process for infused insulin. *Diabetes Care* 1999;22:1371–2.
- [27] Boivin S, Belicar P, Melki V, EVADIAC Group. Assessment of in vivo stability of a new insulin preparation for implantable insulin pumps. *Diabetes Care* 1999;22:2089–90.
- [28] Renard E, Baldet P, Picot MC, Jacques-Apostol D, Lauton D, Costalat G, et al. Catheter complications with implantable systems for peritoneal insulin delivery. An analysis of frequency, predisposing factors and obstructing materials. *Diabetes Care* 1995;18:300–6.
- [29] Melki V, Tall P, Hanaire-BROUTIN H. Intérêt du scanner dans l'exploration des problèmes de cathéter au cours du traitement du diabète par pompe à insuline implantable. *Infusystèmes* 2004;21:17–21.
- [30] Olsen CL, Chan E, Turner DS, Irvani M, Nagy M, Selam JL, et al. Insulin antibody responses after long-term intraperitoneal insulin administration via implantable programmable insulin delivery systems. *Diabetes Care* 1994;17:169–76.
- [31] Jeandidier N, Boivin S, Sapin R, Rosart-Ortega F, Uring-Lambert B, Reville P, et al. Immunogenicity of intraperitoneal insulin infusion using programmable implantable devices. *Diabetologia* 1995;38:577–84.
- [32] Lassmann-Vague V, Belicar P, Raccach D, Vialettes B, Sodoyez JC, Vague P. Immunogenicity of long-term intraperitoneal insulin administration with programmable pumps: metabolic consequences. *Diabetes Care* 1995;18:498–503.
- [33] Jeandidier N, Boullu S, Busch-Brafin MS, Chabrier G, Sapin R, Gasser F, et al. Comparison of antigenicity of Hoechst 21 PH insulin infusion using either implantable intraperitoneal pump or subcutaneous external pump infusion in type 1 diabetic patients. *Diabetes Care* 2002;25:84–8.
- [34] Kessler L, Tritschler S, Bohbot A, Sigrist S, Karsten V, Boivin, et al. Macrophage activation in type 1 diabetic patients with catheter obstruction during peritoneal insulin delivery with an implantable pump. *Diabetes Care* 2001;24:302–7.
- [35] Lassmann-Vague V, Belicar P, Alessis C, Raccach D, Vialettes B, Vague P. Insulin kinetics in type 1 diabetic patients treated by continuous intraperitoneal insulin infusion: influence of anti-insulin antibodies. *Diabet Med* 1996;13:1051–5.
- [36] Hanaire-BROUTIN H, Melki V, Tauber JP. Treatment of acquired immune insulin resistance with i.v. immunoglobulins. *Diabetologia* 1999;42:1378.
- [37] Melki V, Dufaitre-Patouraux L, Hanaire-BROUTIN H, pour le groupe EVADIAC. Prévalence et incidence des maladies auto-immunes chez des diabétiques de type 1 traités par pompe externe ou implantables. *Diabetes Metab* 2003;29:1S50 [Abstract].
- [38] Renard E, Raingeard I, Costalat G, Apostol D, Lauton D, Boulet F, et al. Aseptic peritonitis revealed through recurrent catheter obstructions in type 1 diabetic patients treated with continuous peritoneal insulin infusion. *Diabetes Care* 2004;27:276–7.
- [39] Schade DS, Eaton RP, Friedman NM, Spencer WJ. Normalization of plasma insulin profiles with intraperitoneal insulin infusion in diabetic man. *Diabetologia* 1980;19:35–9.
- [40] Schade DS, Eaton RP, Davis T, Akiya F, Phinney E, Kubica R, Vaughn EA, et al. The kinetics of peritoneal insulin absorption. *Metabolism* 1981;30:149–55.
- [41] Selam JL, Raymond L, Jacquemin JL, Orsetti A, Richard JL, Mirouze J. Pharmacokinetics of insulin infused intra-peritoneally via portable pumps. *Diabetes Metab* 1985;11:170–3.
- [42] Schaepleynck Belicar P, Vague P, Lassmann-Vague V. Reproducibility of plasma insulin kinetics during intraperitoneal insulin treatment by programmable pumps. *Diabetes Metab* 2003;29(4 Pt 1):344–8.
- [43] Nelson JA, Stephen R, Landau ST, Wilson DE, Tyler FH. Intraperitoneal insulin administration produces a positive portal-systemic blood insulin gradient in unanesthetized, unrestrained swine. *Metabolism* 1982;31:969–72.
- [44] Nathan DM, Dunn FL, Bruch J, McKittrick C, Larkin M, Haggan C, et al. Postprandial insulin profiles with implantable pump therapy may explain decreased frequency of severe hypoglycaemia, compared with intensive subcutaneous regimens, in insulin-dependent diabetes mellitus patients. *Am J Med* 1996;100:412–7.
- [45] Oskarsson PR, Lins PE, Backman L, Adamson UC. Continuous intraperitoneal insulin infusion partly restores the glucagon response to hypoglycaemia in type 1 diabetic patients. *Diabetes Metab* 2000;26:118–24.
- [46] Oskarsson PR, Lins PE, Wallberg-Henriksson H, Adamson UC. Metabolic and hormonal responses to exercise in type 1 diabetic patients during continuous subcutaneous, as compared to continuous intraperitoneal, insulin infusion. *Diabetes Metab* 1999;25:491–7.
- [47] Point study group. One-year trial of a remote-controlled implantable infusion system in type 1 diabetic patients. *Lancet* 1988;i:866–9.
- [48] Jeandidier N, Selam JL, Renard E, Guerci B, Lassmann-Vague V, Rocher L, et al., for the Evadiac study group. Decreased severe hypoglycaemia frequency during intraperitoneal insulin infusion using programmable implantable pumps. *Diabetes Care* 1996;19:780.
- [49] Catargi B, Meyer L, Melki V, Renard E, Jeandidier N, for the EVADIAC study group. Comparison of blood glucose stability and HbA1c between implantable insulin pumps using U400 HOE 21PH insulin and external pumps using lispro in type 1 diabetic patients: a pilot study. *Diabetes Metab* 2002;28:133–7.
- [50] De Vries JH, Eskes SA, Snoek FJ, Pouwer F, Van Ballegooye E, Spijker AJ, et al. Continuous intraperitoneal insulin infusion in patients with 'brittle' diabetes: favourable effects on glycaemic control and hospital stay. *Diabet Med* 2002;19:496–501.

- [51] Selam JL, Raccach D, Jeandidier N, Lozano JL, Waxman K, Charles MA. Randomized comparison of metabolic control achieved by intraperitoneal insulin infusion with implantable pumps versus intensive subcutaneous insulin therapy in type I diabetic patients. *Diabetes Care* 1992;15:53–8.
- [52] Haardt MJ, Selam JL, Slama G, Bethoux JP, Dorange C, Mace B, et al. A cost-benefit comparison of intensive diabetes management with implantable pumps versus multiple subcutaneous injections in patients with type I diabetes. *Diabetes Care* 1994;17:847–51.
- [53] Saudek CD, Duckworth WC, Giobbie-Hurder A, Henderson WG, Henry RR, Kelley DE, et al. Implantable insulin pumps vs. multiple dose insulin for non-insulin-dependent diabetes mellitus: a randomized clinical trial. *JAMA* 1996;276:1322–7.
- [54] Renard E, Apostol D, Lauton D, Boulet F, Bringer J. Quality of life in diabetic patients treated by insulin pumps. *QoL Newsletter* 2002;28:11–3.
- [55] Baillot-Rudoni S, Apostol D, Vaillant G, Brun JM, Renard E, on behalf of the EVADIAC Study Group. Implantable pump therapy restores metabolic control and quality of life in type 1 diabetic patients with Buschke's non systemic scleroderma. *Diabetes Care* 2006;29:1710.
- [56] Paulsen EP, Courtney JW, Duckworth WC. Insulin resistance caused by massive degradation of subcutaneous insulin. *Diabetes* 1979;28:640–5.
- [57] Riveline JP, Vantyghem MC, Fermon C, Brunet C, Gautier JF, Renard E, et al. Subcutaneous insulin resistance successfully circumvented on long term by peritoneal insulin delivery from an implantable pump in four diabetic patients. *Diabetes Metab* 2005;31:496–8.
- [58] Renard E, Lauton D, Bonifacj C, Costalat G, Jacques D, Bringer J, et al. Experience with intraperitoneal insulin infusion from implantable programmable systems in type 1 (insulin-dependent) diabetes mellitus previously treated by external pumps. *Diabetes Metab* 1993;19:364–71.
- [59] Liebl A, Frei T. Safety in continuous intraperitoneal insulin infusion CIPHI via DiaPort®: results from the DiaPort-001 study. *Diabetologia* 2003;46(Suppl 2):127 [Abstract].
- [60] Shapiro AM, Lakey JR, Ryan EA, Korbutt GS, Toth E, Warnock GL, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med* 2000;343:230–8.
- [61] Ryan EA, Paty BW, Senior PA, Bigam D, Alfadhli E, Kneteman NM, et al. Five-year follow-up after clinical islet transplantation. *Diabetes* 2005;54:2060–9.
- [62] Belicard P, Jeandidier N, Renard E, Boivin S, Gross P, Pinget M, et al. Implanted insulin pump may represent a chance for young women with unstable type 1 diabetes to give birth. *Diabetes Care* 1999;22:1001–2.