Feasibility of Intraperitoneal Insulin Therapy With Programmable Implantable Pumps in IDDM

A multicenter study

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OBJECTIVE — To report the overall French experience, obtained through the collaboration of seven centers (EVADIAC [Evaluation dans le Diabète du Traitement par Implants Actifs] register), on the safety, feasibility, and efficacy of intraperitoneal insulin therapy by programmable implantable pumps, using three different devices.

RESEARCH DESIGN AND METHODS — This is a multicenter prospective study involving 224 type I diabetic patients implanted with a programmable implantable pump (cumulative follow-up: 353 patient-years; mean duration: 1.5 ± 0.9 years [mean ± SD]). The Infusaid and the Promedos devices are equipped with a side port and refilled with U100 insulin (Hoechst 21 PH); the Minimed pump is not equipped with a side port and is refilled with U400 insulin (Hoechst 21 PH). Metabolic data and adverse events were recorded in a central register run by EVADIAC.

RESULTS — A total of 29 local pump-pocket events (8/100 patient-years) and 9 pump failures (2.5/100 patient-years) occurred. The major technical problems were *1*) pump flow rate reduction related to insulin aggregates, reversible after alkaline rinsing of the pump, and 2) 47 catheter obstructions requiring laparoscopic or conventional surgery. Pump therapy was abandoned in only 11 patients. HbA_{1c} (7.4 ± 1.8 vs. 6.8 ± 1.0%, $P < 0.001$), mean glycemia (8.7 ± 1.5 vs. 7.8 ± 1.0 mmol/l, $P < 0.001$), and blood glucose SDs (3.8 ± 0.8 vs. 3.3 ± 0.8 mol/l, $P < 0.001$) decreased significantly after 6 months and remained lower than baseline thereafter.

CONCLUSIONS — Intraperitoneal insulin infusion using an implantable programmable pump is a feasible and relatively safe technique that may improve metabolic control and glycemic stability. Long-term studies, however, are needed to demonstrate whether or not the improvement in glycemic control could be sustained for several years.

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BMI, body mass index; CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; EVADIAC, Evaluation dans le Diabète du Traitement par Implants Actifs.

Intensive diabetes management by multiple subcutaneous injections or continuous subcutaneous insulin infusion (CSII) is efficient in preventing microvascular complications of type I diabetes, but it increases the risk of severe hypoglycemia (1) and does not completely restore metabolic homeostasis. Intraperitoneal insulin delivery by implantable pumps results in preferential insulin absorption by the portal system (2) and in lower peripheral levels of insulinemia (3). In the future, implantable devices could include a glucose sensor, creating a closed-loop feedback insulin delivery system. Previous studies have reported encouraging results in regard to the safety and efficacy of intraperitoneal insulin infusion, but most of these involved a small number of patients and focused on a single device (4–7). This article reports the results of the overall experience from all French centers through a central register run by the Evaluation dans le Diabète du Traitement par Implants Actifs (EVADIAC) Society.

RESEARCH DESIGN AND METHODS

The study was approved by a French ethics committee, and 224 patients recruited in seven centers gave written consent. The patients' characteristics were age 39 ± 9 years, sex ratio (men:women) 1.3:1, duration of diabetes 19 ± 8 years, and body mass index (BMI) 24 ± 3 kg/m^2 (means ± SD). Selection criteria included type I diabetes with negative response of plasma C-peptide to 1 mg intravenous glucagon, no hypoglycemia unawareness, absence of unstable retinopathy or advanced nephropathy, good compliance with intensive diabetes management (at least 4 home blood glucose tests daily [Glucometer M Memory Meter, Miles, Elkart, IN]), and adherence to treatment goals (i.e., near-normal glycemia, avoidance of severe hypoglycemia, and monthly clinic visits). A total of 111 patients had stable retinopathy, 24 had overt nephropathy, and 46 had symptomatic neuropathy. Before implantation, patients were treated by multiple injec-

Table 1—*Major characteristics of the three pump models*

	Mechanism	Reservoir volume (ml)	Insulin used	Stroke volume (μl)	Weight (g)	Size (cm)	Basal rates (n)
Minimed MIP 2001	Piston negative pressure	15	U400	0.5	160	8 × 2	2
Infusaid model 1000	Accumulator positive pressure	25	U100	1	300	9 × 2.7	6
Siemens Promedos ID3	Piston negative pressure	20	U100	1	165	8 × 2.1	6

Battery life of all three pump models is >3 years.

tions (n = 50), CSII (n = 154), or intraperitoneal insulin infusion using an external pump (n = 20).

From September 1989 to January 1993, 260 pumps were implanted: 205 Minimed MIP 2001 pumps (Minimed Technologies, Sylmar, CA), 48 Infusaid Model 1000 pumps (Shiley Infusaid, Norwood, MA) (8), and 7 Promedos ID3 pumps (Siemens Elema, Micro Infusion Systems, Solna, Sweden). The major characteristics of the three pumps are summarized in Table 1. All devices are designed with a bilaminate catheter with silicone rubber outercoat and are polyethylene lined. Basal and premeal bolus rates were modified by telemetry using a battery-operated programmer. Human insulin, stabilized by a surfactant (HOE 21 PH, Hoechst, Frankfurt, Germany), was used at a concentration of 100 U/ml (Infusaid and Promedos) or 400 U/ml (Minimed).

Surgical pump implantation was performed under local (n = 90) or general (n = 170) anesthesia in the lower left quadrant of the anterior abdominal wall, with the catheter tip free-floating in the peritoneal cavity. Refills were performed every 1 (Infusaid, Promedos) to 3 (Minimed) months. At this time, underdelivery of insulin and device malfunction were indicated by a reduction of the actual flow rate compared with the theoretical rate programmed by the communicator. The rinse procedure used to treat pump slowdowns of Infusaid models has been previously described (6).

Data from memory meters were downloaded to a computer system (Glucofacts Data Management System). Mean blood glucose levels ± SD and glycemic fluctuations expressed as SDs of blood glucose excursions (7) were evaluated over 1 month, at baseline, and every 3 months. Glycated hemoglobin (HbA_{1c}) levels were measured at baseline and every 3 months using high-pressure liquid chromatography (normal values: 4.0–6.0%) (9). The number of ketoacidotic and severe hypoglycemic episodes, as defined by the Diabetes Control and Complications Trial (DCCT) (i.e., requiring assistance), were evaluated retrospectively for the preimplant period and then recorded prospectively at every visit (10). The medical staff were immediately notified by the patient of any adverse events occurring during the study, which were immediately reported to the EVADIAC register.

Statistical analysis

Analysis of variance for repeated measures was used for glycated hemoglobin, mean blood glucose, and SDs of blood glucose excursions. One-way analysis of variance was used to compare pre- and postimplantation severe hypoglycemic episodes.

RESULTS — All the French centers involved in the trial collaborated to collect the following data throughout the study. Cumulative follow-up was 353 patient-years (mean duration: 1.5 ± 0.9 years, range: 1–40 months). A total of 164 patients have been treated for more than 1 year. Among the nine patients implanted for more than 3 years, five had their pump replaced because of expected battery depletion. The complications of implantable pump therapy are summarized in Table 2.

Sixty-five percent of the local pump-pocket events occurred during the first half of the study. There was no case of overdelivery of insulin. Nine pump failures (2.5/100 patient-years) required replacement. A gradual rate of infusion slowdown occurred in all Infusaid pumps after an average of 10 months after implantation. Accumulator volume decreased progressively because of insulin aggregates forming in the ejection chamber. Aggregates were easily dissolved using a basic solution placed in the reservoir and collected back from the side port. Eight cases of backflow of insulin into the reservoir, due to insulin aggregates in the pumping mechanism and leading to underdelivery of insulin, were noticed with the Minimed pump after 2 years of implantation, and one was noticed with the Promedos device, which was replaced. Deterioration of glycemic control due to slowdowns and backflows was always gradual and partly compensated for by an increase in insulin doses.

A total of 47 (13.3/100 patient-years) catheter blockages occurred, resulting in rapid deterioration of diabetes control (incidence rate: 14.5, 12.3, and 17.3/100 patient-years for Infusaid, Minimed, and Promedos models, respectively). Eleven blockages were due to peritoneal adhesions, which were resolved by cleaning the catheter tip during laparoscopic or conventional surgery; 36 cases of total obstruction required catheter replacement. All catheter breakages oc-

Table 2—*Complications of the treatment by implantable pumps*

	n	Per 100 patient-years	Treatment
Pump-pocket events			
Hematomas	4 (M = 4)	1.1	Needle punction
Skin erosions	7 (I = 3, M = 4)	1.9	Surgical repair, contralateral implantation or explantation
Pocket infections	4 (I = 1, M = 3)	1.1	Explantation
Pump migrations	6 (I = 2, M = 4)	1.4	Surgical fixation
Local abdominal pains	9 (I = 3, M = 5, P = 1)	2.5	1 explantation, 1 surgical displacement
Pump failures	9	2.5	Replacement
Electronical failure	3 (I = 1, M = 2)		
Mechanical failure	1		
Premature battery depletion	5		
Catheter-related problems			
Blockage	47 (I = 15, M = 30, P = 1)	13.3	
Peritoneal adhesions	11		Laparoscopic (n = 7) or conventional surgery (n = 4)
Total occlusions	36		Surgical replacement
Migration	3 (I = 1, M = 2)	0.08	Surgery
Breakage	3 (I = 3)	0.08	Surgery
Clinical complications			
Ketoacidosis	11	3.1	
Severe hypoglycemia	9	2.5	

I, Infusaid; M, Minimed; P, Promedos.

curred during the first half of the study. The improved design of the Infusaid catheter eliminated this problem thereafter.

In summary, 36 pumps (10/100 patient-years) were explanted for local or technical problems, and 90 surgical events (25/100 patient-years) were required. Eleven patients were advised to abandon pump therapy as a consequence of local pump-pocket events (n = 6), technical complications such as recurrent catheter obstruction (n = 3), or both (n = 2).

Blood glucose control data are shown in Fig. 1. Glycated hemoglobin (7.4 ± 1.8 vs. 6.8 ± 1.0%, $P < 0.001$), mean blood glucose levels (8.7 ± 1.5 vs. 7.8 ± 1.0 mmol/l, $P < 0.001$), and SDs of blood glucose excursions (3.8 ± 0.8 vs. 3.3 ± 0.8 mmol/l, $P < 0.001$) decreased significantly after 6 months and remained stable thereafter. Frequency of capillary glucose levels below 3.5 mmol/l decreased slightly, but not significantly, after 6 months and returned to baseline values thereafter (data not shown). Eleven ketoacidotic episodes (3.1/100 patient-years) occurred, all but one being directly related to catheter obstructions. The incidence rate of severe hypoglycemic episodes was significantly reduced as compared with the preimplantation period (15.2/100 vs. 2.5/100 patient-years, $P < 0.001$). Two deaths were reported during the follow-up (one from kidney neoplasia and one from thromboembolia). BMI and insulin doses did not vary after implantation.

CONCLUSIONS — Our study confirms the safety, feasibility, and efficacy of implantable-pump therapy. Pump runaway, which is the major safety concern with delivery devices, was totally prevented by the sophisticated electronic design and built-in redundant safety features of the pumps. The incidence rate of pump-pocket events was reduced during the study because of the improvement in surgical practice. The creation of a collaborative society (EVADIAC) of implanting centers provides an effective communication network to evaluate problems, to establish criteria for new centers, and to provide training for health care staff. This support structure may help to reduce problems in the future.

Pump failures occurred at a slightly lower rate (2.5/100 patient-years) than in the Point Study (5.5/100 patient-years) (4) and in the Programmable Implantable Medication System (PIMS) Study (3.6/100 patient-years) (5), indicating that manufacturers have improved their devices. Flow slowdowns were a major problem with the Infusaid model. The rinsing procedure with an alkaline solution was safe and efficient in restoring normal flow rates. Backflows of insulin from the piston to the reservoir occurred in the negative pressure pumps; comparison between the Minimed and the Promedos models was impossible because of the short experience with the latter. Catheter migrations and breakage were totally avoided during the second half of the study by the improvement of

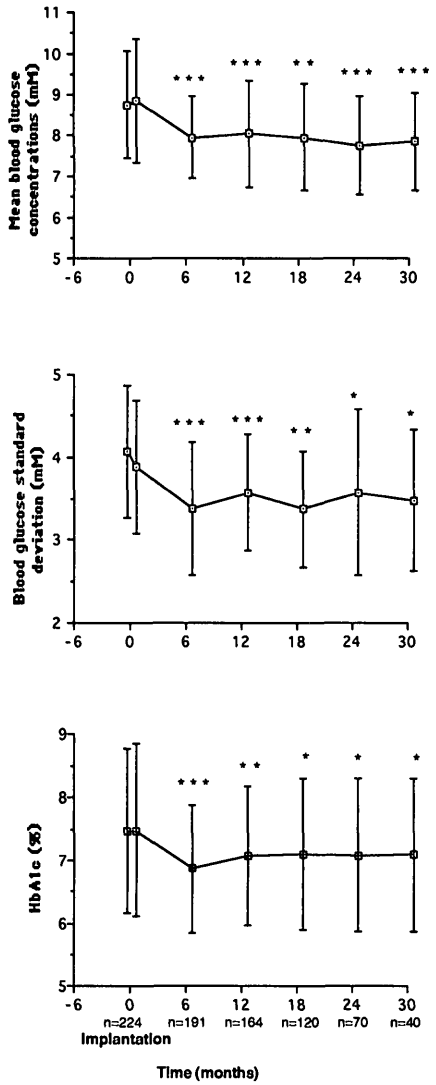

Figure 1—*Mean capillary glucose levels, SDs of blood glucose excursions, and HbA_{1c} levels before and after implantation. Data are means ± SD. *P < 0.05, **P < 0.01, ***P < 0.001 vs. baseline values.*

surgical practice and change in catheter configuration. However, catheter obstructions remained a major problem. The frequency (13.3/100 patient-years) was lower than in the Point study (27.7/100 patient-years) (5) and comparable with the PIMS Study (14.2/100 patient-years) (5) despite a longer duration in our trial. The incidence rate was not different with the Infusaid and the Minimed devices. The experience with the Promedos pump is too short to evaluate catheter occlusion risk.

Although metabolic control was good before implantation, it improved further after implantation, with no increase in hypoglycemic events and a reduction of blood glucose fluctuations, as previously shown (6,12). The incidence of ketoacidosis was comparable with the frequency reported in the DCCT standard and experimental groups, respectively 3.0 and 2.7 events per 100 patient-years (1). Importantly, as already reported (11), the rate of severe hypoglycemia (2.5/100 patient-years) was dramatically lower than in the DCCT experimental group (62/100 patient-years) and even the standard group (19/100 patient-years) (1), although better glycemic control was maintained in our study.

In summary, the EVADIAC results show that intraperitoneal insulin infusion, using an implantable programmable device, is a feasible and safe technique in a large patient group. Very few patients withdrew from the study, and all patients decided to have a new pump implanted when their first pump reached the natural battery depletion. The metabolic data collected show a better efficacy of the insulin delivery system combined with a decreased rate of severe hypoglycemic events when compared with subcutaneous insulin therapy. Nevertheless, technical problems, such as reduction in the pump flow rate due to insulin aggregates and catheter obstructions, still require improvements to allow precise detection, prevention, and treatment. As with any new technique, a rapid communication between groups as provided by EVADIAC is an important factor in success. Now that the feasibility and the safety of the therapy are well established, important aspects still require evaluation, such as the comparison of continuous intraperitoneal insulin infusion by implantable pumps with intensive subcutaneous insulin therapy in terms of cost, quality of life, and prevention or stabilization of long-term diabetic complications.

APPENDIX

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