Long-Term Therapy of IDDM With an Implantable Insulin Pump

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OBJECTIVE — To examine the long-term benefits and risks of treatment of IDDM with an implantable programmable insulin pump.

RESEARCH DESIGN AND METHODS — Seventy-six patients with IDDM were studied at nine clinical centers. After 3–4 months of intensive subcutaneous therapy, the Infusaid Model 1000 pump was implanted, and insulin was delivered either intraperitoneally or intravenously for an average of 39.6 ± 10 months (251 patient-years). Data was collected for glycemic control, lipid levels, weight gain, insulin requirements, adverse events, and quality of life. Sixty-three patients were also followed for 8.5 ± 6.3 months (45 patient-years) after pump therapy was discontinued.

RESULTS — Mean quarterly HbA_{1c} fell with subcutaneous intensive therapy and remained stable on implantable pump therapy between 6.9 and 7.5%. Severe hypoglycemia was relatively rare, with only 4 episodes/100 patient-years of implantable pump therapy. This rate was significantly less than with subcutaneous intensive therapy before implantable pump initiation (33 episodes/100 patient-years) or after discontinuation of implantable pump therapy (36/100 patient-years) ($P < 0.003$). Weight did not increase significantly in the 1st year of therapy, but increased by 2.0 ± 4.3 kg after 3 years of therapy. There were no significant differences in metabolic control or adverse events between intraperitoneal and intravenous insulin therapy except for minor differences in lipid levels and the more frequent development of catheter obstruction with intravenous delivery. Most pump slow-downs and catheter occlusions were corrected noninvasively. Quality of life, as measured by the Diabetes Control and Complications Trial instrument, showed high satisfaction and improved impact scores.

CONCLUSIONS — Long-term implantable pump therapy maintained HbA_{1c} in a range similar to intensive subcutaneous therapy, but with fewer episodes of severe hypoglycemia. Although pump and catheter occlusions remain a limitation, patient satisfaction with implantable pump therapy remains high.

The results from the Diabetes Control and Complications Trial (DCCT) emphasize the importance of glycemic control in patients with IDDM for prevention of long-term complications (1). However, current methods of intensive therapy are often associated with increased risk of severe hypoglycemia, excessive weight gain, and poor patient acceptance. Preliminary reports from short-term trials (12–18 months) suggest that implantable insulin pump therapy may ameliorate some of these problems (2–4). In this report, we describe the long-term results of a multicenter study of implantable pump therapy in IDDM, including metabolic control, lipid levels, weight gain, insulin requirements, type and frequency of adverse events, and quality of life.

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DCCT, Diabetes Control and Complications Trial.

RESEARCH DESIGN AND METHODS

— The design of the study has been previously described (4). Patients were treated for a minimum of 3 months with intensive subcutaneous regimens (greater than or equal to three injections or continuous subcutaneous insulin infusion) before starting therapy with the Infusaid Model 1000 implantable programmable pump. The route of insulin delivery (intraperitoneal or intravenous) was the choice of the individual center.

Subjects

Seventy-six patients with IDDM were recruited from eight centers in the U.S. and one in Italy. These centers followed a common protocol and are therefore analyzed together for this report. Results from additional centers in France have been reported as part of the EVADIAC study (5). The demographic characteristics of the study population at baseline are shown in Table 1.

Outcome data

The occurrence of severe hypoglycemia and diabetic ketoacidosis, using the DCCT definitions (1), pump and catheter malfunction, and issues related to pump maintenance, were recorded monthly. HbA_{1c} was measured monthly during the 1st year and quarterly thereafter. In addition, self-monitored glucose profiles obtained with a memory meter were downloaded monthly to computers at each clinic. Fasting lipid profiles were required at study entry, at implant, and after 6 and 12 months of implantable pump therapy and were elective after 24 and 36 months of therapy. Quality of life was assessed longitudinally with the DCCT quality of life instrument (6).

Assays

HbA_{1c} was measured with a high performance liquid chromatography assay at a central laboratory (Massachusetts General Hospital) for all U.S. centers (7) and separately at the Italian center. The correlation between the two assays was $r = 0.99$ ($P < 0.001$), with an absolute mean difference <0.4%, based on split duplicate samples ($n = 30$). The results of the two assays are

Table 1—*Baseline characteristics*

n	76
Age (years)	37 ± 8
Sex (% women)	51
Duration IDDM (years)	15 ± 8
Percentage ideal body weight	107 ± 11
Previous use of intensive therapy	85
HbA_{1c} (%)	7.87 ± 1.5

Data are means ± SD or %.

reported without transformation. Lipid levels were measured locally.

Statistical analysis

All results are stated as means ± SD, unless noted otherwise. Within-patient changes in HbA_{1c} and glucose over time were examined using Wilcoxon's signed-rank tests. For weight, lipid levels, and insulin dose, a slope was constructed for each patient, and the mean slopes across all patients were examined with a signed-rank test. Intravenous and intraperitoneal insulin delivery results were compared using rank sum procedures and linear regression models.

RESULTS — After 3–4 months of subcutaneous intensive therapy (24 patient-years), 56 patients in the U.S. and 20 in Italy were treated with implantable pump therapy for 39.6 ± 10 months (range 4–58 months), for a total of 251 patient-years. Fifty-eight patients completed at least 3 years of study.

Fifty-one patients were administered insulin exclusively by the intraperitoneal route during the study. Twenty-five patients (all in U.S.) were administered insulin by the intravenous route; 17 of these patients changed from intravenous to intraperitoneal delivery after an average of 12.8 ± 8.8 months because of recurrent intravenous catheter obstructions, catheter migration, and/or vein thrombosis (8). A comparison of the three patient subgroups (intraperitoneal only, intravenous only, and intravenous changed to intraperitoneal) revealed no significant differences with regard to age, sex, percent ideal body weight, or level of HbA_{1c} at time of enrollment (data not shown). The metabolic results of the group that changed from intravenous to intraperitoneal delivery were ascribed to the route of delivery at the time of measurement. Experience with intraperitoneal and intravenous insulin delivery with the implantable pump was 213 and 38 patient-years, respectively.

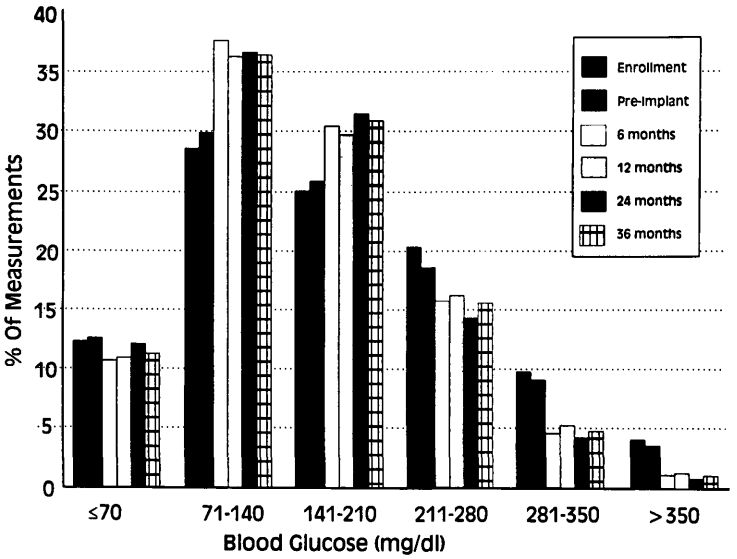

Figure 2—*Distribution of self-glucose monitoring results, collected on memory blood glucose meter and transferred to a computer at the clinical centers, during intensive subcutaneous therapy (−3 and 0) compared with implantable pump therapy (months 6, 12, 24, and 36).*

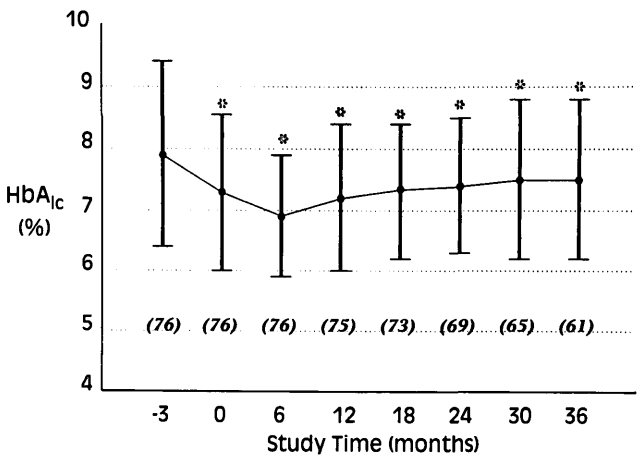

Figure 1—*HbA_{1c} (mean ± SD) for all intraperitoneally and intravenously treated patients. At least 3 months of intensive subcutaneous therapy (−3 to 0 months) preceded treatment with implantable pump therapy. The number in parentheses reflects the number of patients with measurements during the previous 6 months. *P < 0.05 compared with time −3 months.*

Mean HbA_{1c} results are shown in Fig. 1 for the entire study cohort. At study entry, mean HbA_{1c} was 7.9 ± 1.5%, reflecting the high prevalence of intensive therapy before entering the study. After 3 months of intensive subcutaneous therapy, HbA_{1c} decreased significantly to 7.3 ± 1.3%. During implantable pump therapy, mean HbA_{1c} fell to a nadir of 6.9 ± 1.0% after 6 months and remained relatively stable at <7.5% during the 3 years. There was no significant difference in HbA_{1c} levels between patients treated with intravenous and intraperitoneal therapy (data not shown).

The HbA_{1c} data from the patients in the U.S. centers were also analyzed separately from the Italian patients because they provided the best comparison to the population in the DCCT and because the HbA_{1c} assay used by the U.S. centers was virtually identical to the DCCT assay (7,9). Mean HbA_{1c} was 7.5 ± 1.5% at study entry, and decreased significantly to 7.1 ± 1.1% after 3–4 months of intensification of subcutaneous insulin therapy. Six months after initiating implantable pump therapy, mean HbA_{1c} decreased to 6.7 ± 1.1% and then stabilized at 7.1% for the remainder of the trial.

The distribution of self-monitored blood glucose results is shown in Fig. 2. More than 75% of all blood glucose measurements were <210 mg/dl at all times during implantable pump therapy, compared with 65% at enrollment and 69% during the 3 months of intensive subcutaneous therapy. The percentage of measurements <70 mg/dl was not different during subcutaneous intensive therapy than during implantable pump treatment. There was no difference in the distribution of blood glucose results for intraperitoneal versus intravenous implantable pump (data not shown).

The incidence of severe hypoglycemia was 33 episodes/100 patient-years during subcutaneous intensive therapy and 4 episodes/100 patient-years during implantable pump therapy ($P < 0.003$). (This incidence of hypoglycemia does not include events during pump and/or catheter flushing procedures, which occurred in the clinic under close supervision and monitoring.) The rate of severe hypoglycemia was greater during intravenous therapy (13 episodes/100 patient-years) than during intraperitoneal therapy (2 episodes/100 patient-years) ($P < 0.05$, intraperitoneal versus intravenous). Sixty-three patients discontinued implantable pump therapy, usually because of the end of pump battery life, and were followed for an additional 45 patient-years after reinitiating intensive subcutaneous therapy. During this period, incidence of severe hypoglycemia was 36 episodes/100 patient-years. Only one case of diabetic ketoacidosis occurred during the trial, during the transition from subcutaneous to implantable pump therapy.

Lipid profiles for the entire study cohort during 3–4 months of intensive subcutaneous therapy were associated with a significant decrease in total cholesterol levels (174.1 ± 30 vs. 182.8 ± 35.1 mg/dl, $P < 0.05$) and HDL cholesterol levels (53.1 ± 15.1 vs. 56.1 ± 16.4 mg/dl, $P < 0.05$). Triglyceride and LDL cholesterol levels did not change significantly during this period.

Lipid profiles were obtained in 98% of the intraperitoneally treated patients at 12 months, 59% at 24 months, and 64% at 36 months. The Wilcoxon's signed-rank tests of slopes from study entry and from preimplant through month 36 were not significantly different from 0 for total cholesterol, LDL cholesterol, and triglyceride levels. The signed-rank test of slopes for HDL cholesterol indicated a slight decline during the course of intraperitoneal therapy (54.1 ± 15.4 mg/dl preimplant, 50.2 ± 14 at 12 months, 53.6 ± 14.1 at 36 months, $P < 0.05$). The triglyceride level increased transiently with intraperitoneal therapy (92.8 ± 39.7 at 12 months vs. 75.7 ± 32 mg/dl preimplant, $P < 0.05$), but then returned toward baseline (84.1 ± 42 at 36 months vs. 84.4 ± 49.4 mg/dl at study entry). There were no significant differences in lipid levels during 12 months of intravenous therapy (86% lipid profiles obtained at 12 months). The only significant difference between intravenous and intraperitoneal therapy was a lower HDL cholesterol and higher triglyceride at month 12 for the intraperitoneal group.

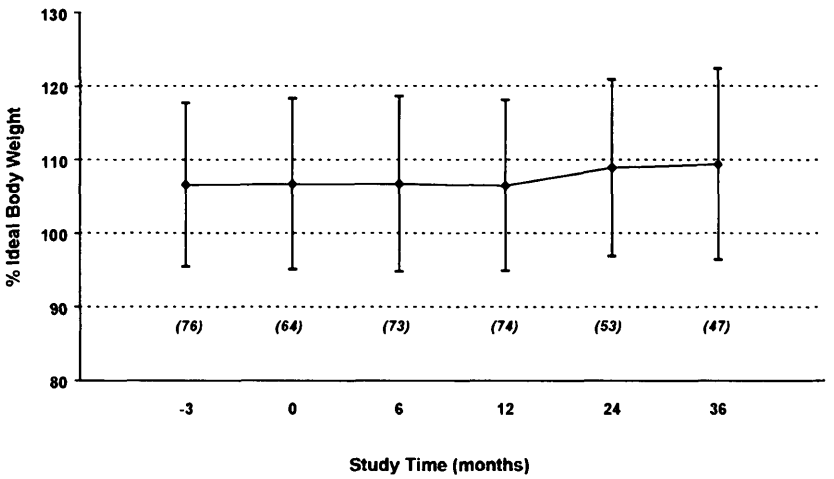

Figure 3—*Mean ± SD percent ideal body weight for patients. The change in ideal body weight over the 36 months of the study was significant (P < 0.01 by Wilcoxon's signed-rank test of slopes). Number in parentheses indicates number of patients measured during the preceding 6 months.*

The change in body weight from baseline is shown in Fig. 3. Weight did not increase from study entry during the 1st year of therapy, but was significantly increased over 36 months ($P < 0.01$, signed-rank test). The mean percent of ideal body weight was 106.6 at entry into the study and 106.7 after 3 months of subcutaneous intensive therapy. By 36 months, percent of ideal body weight was 109.4 ± 13.0. This change represents a gain in weight of 2.0 ± 4.3 kg at 36 months. New cases of obesity (>120% ideal body weight) occurred at the rate of 3.8/100 patient-years of implantable pump therapy.

Daily insulin dose was 0.67 ± 0.19 U/kg in the 68 intraperitoneally treated patients at baseline and did not change during the study. Similarly, the total daily insulin dose remained stable during the course of the study (47 ± 16 U/day at –3 months; 47 ± 15 at initiation of pump therapy; and 48 ± 19, 51 ± 23, and 45 ± 14 U/day at 12, 24, and 36 months of pump therapy, respectively). The daily insulin dose in intravenously treated patients was not significantly different from the dose with intraperitoneal delivery.

The types of technical complications accompanying the implantable pump have been reported elsewhere (4,10,11). The most common technical problem was pump slow-down, presumably secondary to aggregation of insulin in the pump flow path, which occurred on average every 9–10 months. Catheter obstruction occurred in 76% of intravenously treated patients after an average of 8.9 ± 6.5 months of therapy and in 81% of intraperitoneally treated patients after 20.6 ± 12 months. The pump and catheter flush procedures worked almost uniformly to correct these problems (10). Irreversible catheter occlusion ultimately requiring surgical intervention (laparoscopy or catheter replacement) occurred in 44% of patients. The major reason for termination of implantable pump therapy in the patients treated with intraperitoneal delivery was battery depletion. Four of the eight patients treated with an intravenous catheter during the entire study terminated treatment before battery depletion because of catheter-related problems. A life table indicating the duration of pump therapy for all patients is shown in Fig. 4.

Several quality-of-life measures, assessed using the instrument developed by the DCCT (6), improved during the study. Specifically, an analysis of the change

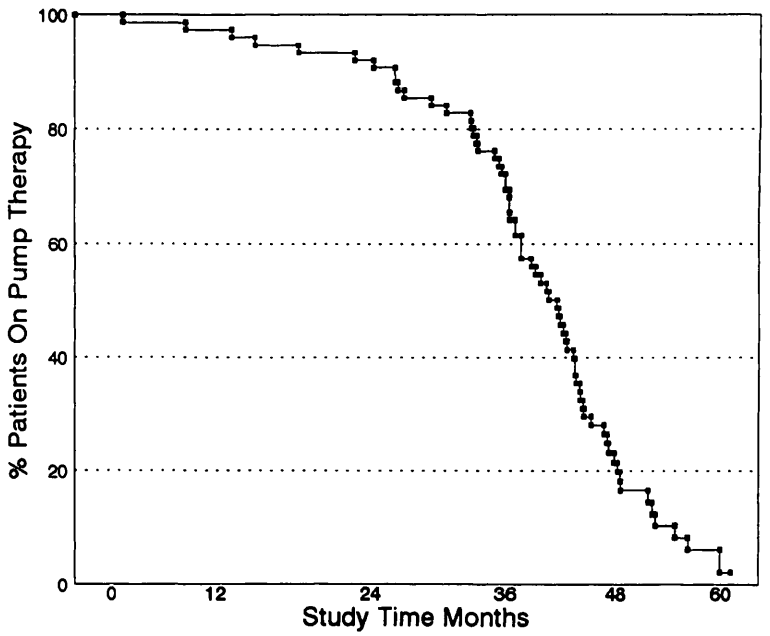

Figure 4—*Life table of implantable pump therapy during study.*

by the signed-rank test revealed a significant improvement in satisfaction between study entry (−3 month) and implant (time 0), which remained stable during implantable pump therapy. The impact scores improved significantly between study entry and time 0 and improved further during implantable pump therapy ($P < 0.05$) (data not shown).

CONCLUSIONS — The importance of intensive therapy in IDDM has been firmly established by the DCCT (1). However, intensive therapy, as practiced by the DCCT, has several limitations, including increased frequency of severe hypoglycemia, weight gain, and the requirement for a high level of patient compliance to the demands of frequent injections, monitoring, and the other elements of intensive therapy. The current generation of implantable pumps do not have a glucose sensor and therefore remain dependent on self-blood glucose monitoring and intensive patient self-care. As documented in this study, they are capable of achieving and maintaining similar levels of metabolic control over time as subcutaneous intensive therapy. The major difference in therapy was the markedly reduced occurrence of severe hypoglycemia. The explanation for this phenomenon is not known, but may reflect the more rapid clearance of insulin when delivered intravenously or intraperitoneally compared with subcutaneously (12). The apparent lower risk of severe hypoglycemia with intraperitoneal therapy compared with intravenous therapy may be related to less negative glucose balance during hypoglycemia, as a consequence of lower peripheral insulin levels with intraperitoneal insulin delivery (13).

The two different routes of insulin delivery provided the opportunity to determine whether the more physiological delivery of insulin directly into the portal system with intraperitoneal catheters has beneficial metabolic effects compared with systemic delivery. Short-term studies have suggested that intraperitoneal delivery may achieve more physiological control of glycemia and lipids (14). The long-term data in the current study does not suggest a significantly different effect of the route of delivery on HbA_{1c} levels or distribution of blood glucose results. Lipid levels were in the normal range and did not change substantially after the initial period of subcutaneous intensive therapy with intravenous delivery. With intraperitoneal delivery, HDL cholesterol decreased and triglycerides increased modestly and transiently, though remaining well within the normal range. This finding is consistent with other studies of intraperitoneal insulin delivery (15–17) and is probably related to amelioration of the persistent compositional abnormalities of the triglyceride-rich and high-density lipoproteins observed with intensive subcutaneous insulin therapy (18–20). The mechanism responsible for this improvement with intraperitoneal therapy compared with subcutaneous therapy is thought to be related to decreased peripheral hyperinsulinemia, resulting in normalization of cholesterol ester transfer and lipoprotein lipase activity (17). Another major difference between the intravenous and intraperitoneal delivery routes was the longer period of intraperitoneal catheter function before obstruction.

The frequency of weight gain (new cases >120% of ideal body weight) encountered with implantable pump therapy (3.8 cases/100 patient-years) was lower than the frequency reported with subcutaneous intensive therapy in the DCCT (12.7 cases/100 patient-years) (1). Whether the lower frequency of weight gain in the current study cohort, compared with the DCCT intensive therapy, was secondary to the high prevalence of subcutaneous intensive therapy before implantable pump therapy (i.e., the subjects had already gained weight with prior subcutaneous intensive therapy) or to some other factor associated with implantable pump therapy is unknown. The frequency of diabetic ketoacidosis with implantable pump therapy, 0.4 episodes/100 patient-years, was less than the 1.8 episodes/100 patient-years reported with intensive therapy in the DCCT (1).

The current study suggests that implantable pump therapy is an effective alternative to subcutaneous intensive therapy. It can achieve similar long-term metabolic control as in the DCCT, but with a lower frequency of severe hypoglycemia and possibly less weight gain. Catheter and pump obstruction was a recurrent problem, but most could be corrected noninvasively, and patient satisfaction with this form of therapy remained high throughout the study.

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APPENDIX

Implantable Insulin Pump Trial Study Group

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