Factors Involved in Catheter Obstruction During Long-Term Peritoneal Insulin Infusion

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OBJECTIVE— To analyze the efficacy of ECPII and the factors responsible for technical problems often encountered. This treatment has been in use with IDDM patients since 1980.

RESEARCH DESIGN AND METHODS— Forty-four IDDM patients were treated by ECPII for 42–78 mo (mean, 53 mo).

RESULTS— Glycemic equilibrium was improved during treatment (mean plasma glucose level, 7.6 mM; mean GHb level, 8%). Catheter blockage was the main reason for ECPII failure (74%). Mean catheter survival of each catheter, determined by actuarial analysis, was 11.7 mo and significantly decreased with subsequent implantation. SEM of the catheter tips showed deposits composed of fibrin and cells occluding the inner lumen. Factors such as age, sex, local infection, and low insulin basal rate were not found to have any incidence on the catheter survival. Placement of the catheter in the upper part of the peritoneum, however, increased catheter survival. Anti-insulin antibodies did not seem to be directly involved in blockage.

CONCLUSIONS— We conclude from this long-term experience that during ECPII, catheter blockage remains the major recurring complication, probably involving a local immune-inflammatory response in the peritoneum.

Initially proposed in 1980 (1,2), ECPII is an efficient route of insulin delivery (3–5). However, technical problems arise during long-term treatment. The objectives of this study, based on 196 patient-yr of ambulatory chronic treatment, were to evaluate clinical factors involved in catheter obstruction, the main obstacle of the intraperitoneal route.

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IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; ECPII, EXTERNAL CONTINUOUS PERITONEAL INSULIN INFUSION; ELISA, ENZYME-LINKED IMMUNOSORBENT ASSAY; SEM, SCANNING ELECTRON MICROSCOPY.

RESEARCH DESIGN AND METHODS

RESEARCH DESIGN AND METHODS— Forty-four IDDM patients (21 men, 23 women; mean age, 39.0 ± 1.7 yr) were treated during an average 53.5 ± 2.8 mo (range 42–78 mo) with insulin infused by means of a portable pump: 181 catheters were successively implanted, and all 44 patients had at least four catheters during the period of study. The mean duration of IDDM was 21.3 ± 1.4 yr. Patients were selected on the basis of their degree of severe primary glycemic instability (4), and all gave informed consent.

Four types of portable pumps were used: the Promedos E1 (Siemens AG, Erlangen, Germany), the MRS 1 (Biomedic, Burgdorf, Switzerland), the Minimed 504 S, and the Nordisk Infusor (Nordisk, Chartres, France). Two porcine insulins were used: U 40 acidic insulin (Hoechst AG, Gif sur Yvette, France) and U 100 neutral insulin (Organon, Saint Denis, France). Each patient selected for this study was treated with exclusively one type of insulin. The catheter was a polyethylene tube coated with silicon (Siemens AG). Since 1986, short catheters (8–10 distal portion) have been used to set the tip in the upper peritoneum as often as possible. The catheters were inserted into the peritoneal cavity under local anesthesia, using a blind needle technique (5), and were X-rayed to control their placement. The X-rays revealed that some catheters were implanted in the upper part of the peritoneum and others in the lower part. However, in 14 patients who presented frequent episodes of obstruction, a laparoscopy was performed to observe the state of the omentum and to place another catheter in a region of the peritoneum free of adherences. According to the principles expressed in the Declaration of Helsinki, the laparoscopy was never used before treatment.

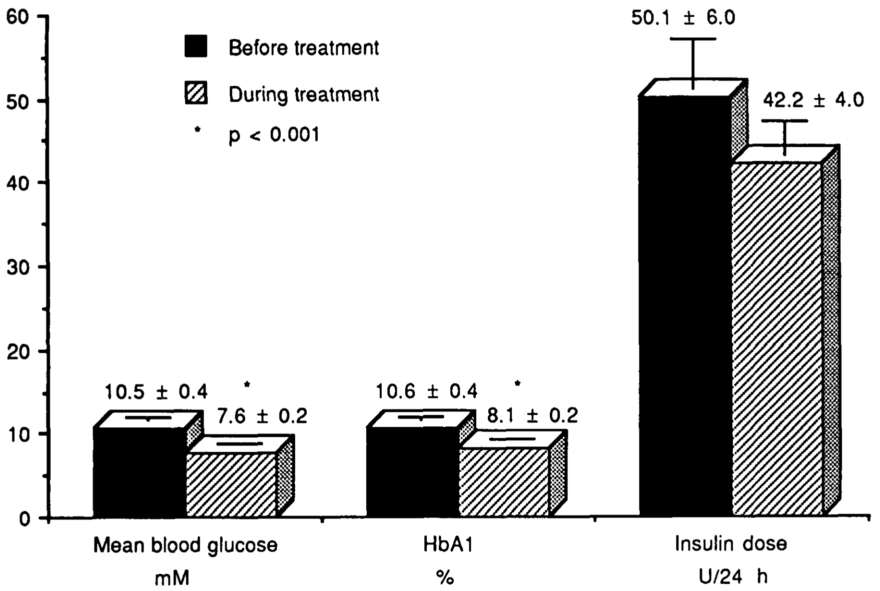

Figure 1—*Blood glucose level, HbA_1, and daily insulin requirements before and during pump treatment.*

Data collection

During infusion, capillary blood glucose was assessed 4–6 times daily (Glucometer M, Miles, Elkhart, IN), and glycemia and insulin requirements were recorded. Both basal and prandial rates were adapted to maintain pre- and postprandial glycemic values between 3.9 and 7.8 mmol, respectively. GHb levels were measured every 2 mo (Quick-sep, Isolab, Akron, OH). Routine physical examinations, plasma C-peptide, lipid measurements, and ophthalmological evaluations were performed every 6 mo (data not shown).

Obstruction of the catheters was suspected clinically when the patients presented hyperglycemia and/or required increasing doses of insulin for several days. Of the apparently obstructed catheters, 25% were X-rayed after injection of radioselectan contrast agent; among the other catheters, we examined the tips of 51 by SEM with a Cambridge Stereoscan model 100. For controls, catheters perfused with each form of insulin tested also were examined.

We have analyzed whether clinical factors such as sex, age, local subcutaneous infections, or low insulin basal rate (<15 U/day) could be related to a higher incidence of obstruction. The main catheter lifetime was calculated for all catheters placed in the upper or lower peritoneum.

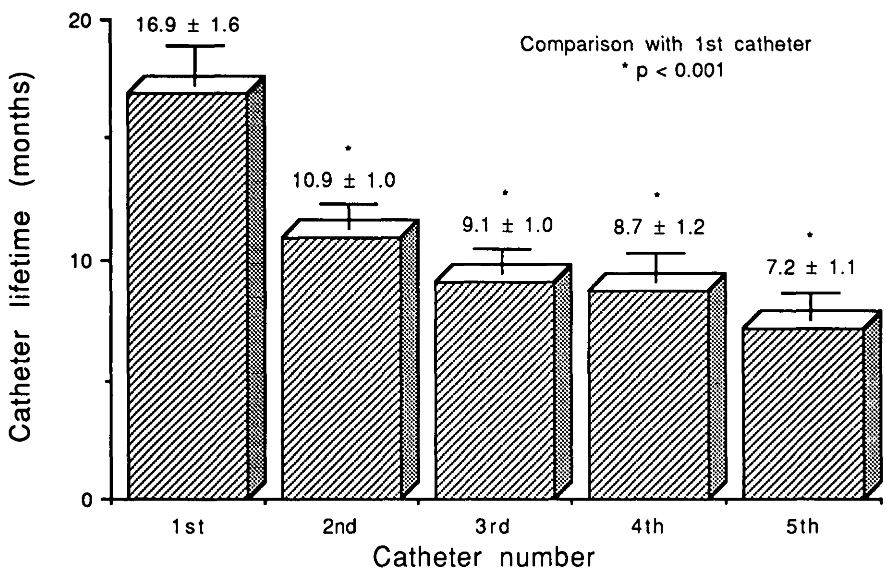

Figure 2—*Mean catheter lifetime of successive peritoneal catheters in the 44 patients; comparison with the first catheter.*

Peritoneal fluid and serum were taken simultaneously for determination of anti-insulin antibody titers by indirect ELISA. Both antigens (Hoechst and Organon insulins) were tested. Peritoneal fluid and serum from nondiabetic women (n = 10) who had undergone laparoscopy for sterility served as a control.

Statistical analysis

All data were computed using the Statistical Analysis System computer package (SAS Institute, Gregy sur Yerves, France) and Bioanalysis Medical Data Package (University of California, Berkeley). Glycemic values were analyzed by paired and unpaired Student's t tests, and mean regression was used to correlate data. The operating life of the catheters was determined by actuarial analysis. Patient subgroups were identified by cluster analysis of cases; the Euclidian measure of distance was used (6).

RESULTS— Mean blood glucose and HbA_1 levels decreased significantly during the period of external pump treatment; the daily insulin requirement also decreased with peritoneal infusion, but

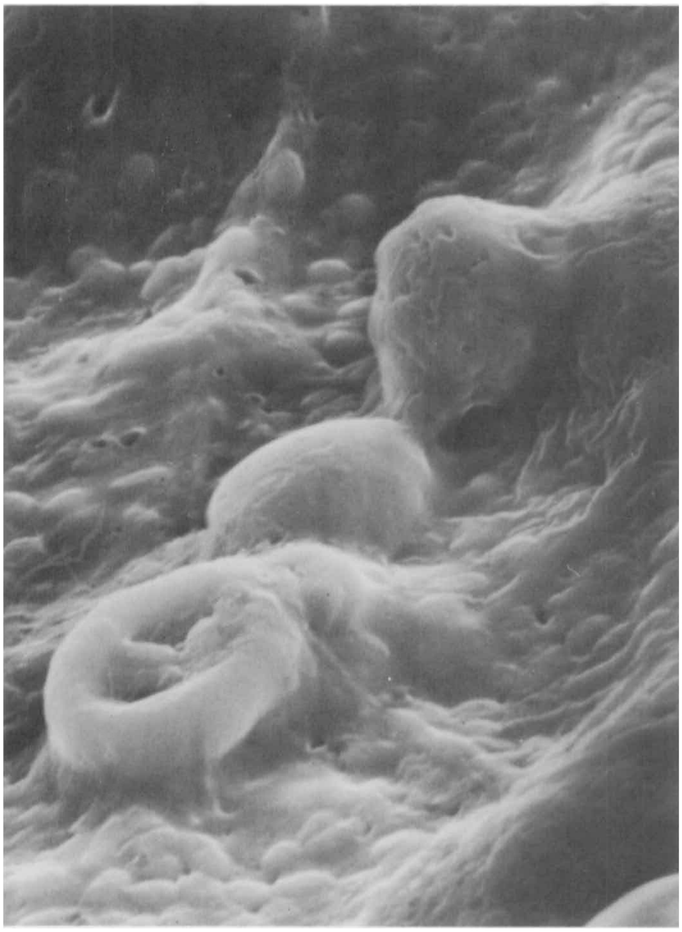

Figure 3—*Scanning electron photomicrograph of the tip of an obstructed catheter; erythrocytes, fibrin node, and perhaps lymphocytes are observed.*

this difference was not significant (Fig. 1).

The mean survival time of a catheter was 11.7 ± 0.6 mo (range 4–36 mo). Statistical analysis of the lifetime of successive individual catheters revealed that catheter survival significantly decreased with subsequent implantation ($P < 0.001$: comparison with the first catheter) (Fig. 2).

The causes of catheter removal were multiple. Among the 181 catheters implanted in the peritoneal cavity, 47 were permeable but had to be removed because of persistent subcutaneous infection (in 26 cases), because of irreparable breaks of the outer portion of the catheter (in 17 cases), or because of abdominal pain related to local peritonitis (in 4 cases). In these latter 4 cases, peritonitis resolved without sequelae after catheter removal and antibiotic therapy. Obstruction was encountered in 134 cases and represented the main cause of catheter removal. X-ray analysis of 33 of them revealed that in 5 cases, a small amount of contrast agent passed through the catheter and opacified a 2- to 3-cm pocket, formed by peritoneum adhering to the tip. In these cases, the tip was free of any deposit; in the other 28 cases, the tip of the catheter was obstructed, and consequently no X-ray pictures could be obtained. Among the 101 catheters that were not X-rayed, 51 were chosen at random for SEM. The analysis showed that the tip sections were occluded by a material adhering to the lumen. This deposit was present up to 1–2 cm from the tip (Fig. 3). Furthermore, only a thin film was present up to 3 cm from the polyethylene tip. The deposits contained laminar structures, cellular fragments, erythrocytes, and spheroid formations (Fig. 3); that these latter formations might be lymphocytes was shown by histological studies (R.B.-R., unpublished observations). Control catheters perfused with insulin did not show any anomalies. No correlation could be shown between the incidence of catheter obstruction and factors such as age, sex, basal insulin rate, or local infection. Mean survival time of the catheters in the upper part of the peritoneum was significantly higher than for those in the lower part, 10.9 ± 0.7 and 6.5 ± 0.6 mo, respectively ($P < 0.001$).

Evaluation of the antibody response revealed natural anti-insulin antibodies in the peritoneal fluid and in the serum of the control group (7,8). Higher antibody titers were found in diabetic patients, but no difference was found between the anti-insulin levels in the peritoneum and the serum. The results were the same regardless of the type of insulin used in the indirect ELISA technique (Fig. 4).

CONCLUSIONS— Based on our long experience in treating IDDM patients by ECPII, we selected 44 patients to evaluate the adverse events that occurred over this period. In contrast to the difficulties encountered by other investigators, we only observed 4 episodes of local peritonitis 4–8 mo after catheter implantation; they all resolved medically after catheter explantation and antibiotic therapy. The main cause of this peritonitis was wounding of the intestine by the catheter tip and not the progression of a subcutaneous infection. Aseptic refilling was taught to the patients, and they all used sterile dressing every day. Catheter

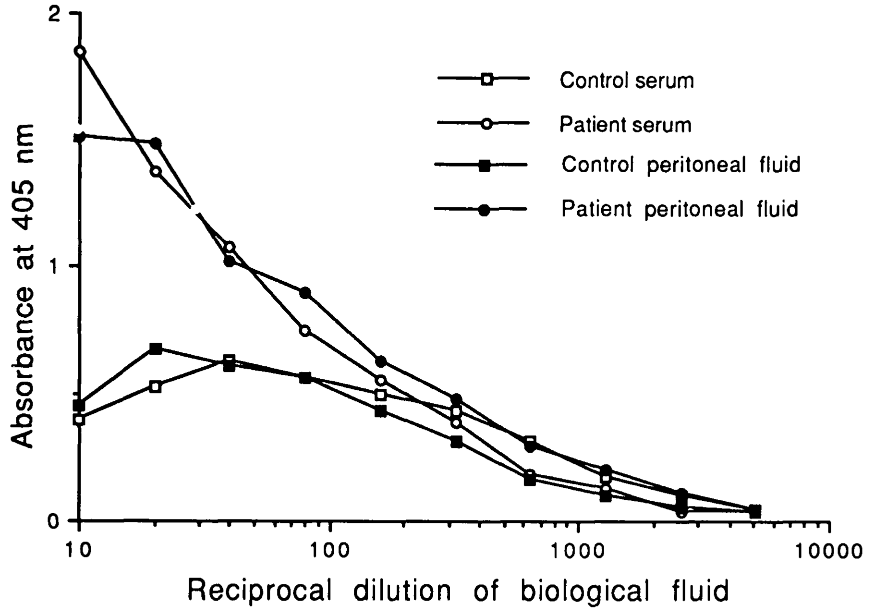

Figure 4—*Anti-insulin antibody titers in the serum and peritoneal fluid of healthy control subjects and diabetic patients.*

breakage of the outer portion accidentally occurred, and this adverse event was related to the portable material.

Catheter obstruction represented the major cause (74%) of catheter removal. The term catheter obstruction masks, in fact, two different problems. The first problem is encapsulation of the tip of the catheter (often lower catheters) by the omentum, therefore preventing insulin from circulating normally and resulting in increasing doses of insulin for days or weeks. Flushing these catheters revealed that they were permeable; when a contrast agent was used, we observed a 2- to 3-cm pocket formed by the omentum. SEM showed that the polyethylene tip was free of any deposit. These results have already been reported for totally implanted devices (9). The second problem, and by far the most frequent, is catheter blockage that is impossible to flush with a fibrinolytic diluent (11).

The main result of our study is that catheter survival decreased with subsequent implantation (suggesting a possible peritoneal immunological reaction to the implanted catheter). SEM of the tip clearly showed that blockage occurred progressively with formation of successive layers of material lining the lumen. The presence of cells indicates that a reflux is possible along the polyethylene tip. The nature of the deposits have been analyzed, and at present insulin and fibrin have been found (3,5) as well as macrophages and lymphocytes. The latter might play a role in the genesis of plug formation. Investigations on the polyethylene tips of explanted catheters from our totally implanted devices have shown similar pictures (R.B.-R., unpublished observations).

On the other hand, anti-insulin antibodies in the peritoneal fluid do not seem to be involved in decreased catheter survival because the antibody levels were similar in the peritoneal fluid and in the serum. In a previous study (10), we reported an increase in the anti-insulin antibody serum titer during continuous peritoneal insulin infusion. Therefore, the intraperitoneal route itself might influence the antibody response without either adverse effects on glycemic equilibrium (because the insulin requirements decreased) or on the incidence of obstruction.

Other factors suspected of being involved such as age, sex, low basal rate of insulin, or infection were not found to play any role in catheter blockage. However, probably because of an improvement in insulin circulation, the upper peritoneum seems to be the best site for catheter placement. Furthermore, we implanted short catheters directly on the surface of the liver by using laparoscopy (R.B.-R., unpublished observations).

Several attempts to blow out the plug occluding the catheter tip have met with success especially when an alkaline buffer solution is used (11); but in our experience, catheter blockage recurred 3–4 wk later. To avoid insulin precipitation in the catheters, several studies have been performed (12–14). Further investigation is needed because insulin often is still found in the catheter tip (9).

Indeed, regardless of whether portable or totally implantable pumps are used, setting a catheter into the peritoneum generates a complex reaction probably involving both an immunological process and coagulation factors. This major problem needs to be resolved before the wide development of this otherwise successful technique.

In summary, the peritoneal delivery of insulin with an external pump results in sustained normalization of glycemic control, but the main limiting obstacle is catheter blockage either by encapsulation or deposits occluding the lumen. The recurrence of this complication needs further study on the materials and the peritoneal reaction.

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