Long-term Continuous Intraperitoneal Insulin Infusion with an Implanted Remote-Controlled Insulin Infusion Device

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SUMMARY
This is a report of the implantation and first 100-day operation using a remote-controlled programmable insulin infusion device in an insulin-dependent diabetic. To prevent insulin aggregation, a special surface-active polymer developed by Hoechst AG, Frankfurt, was used as an additive.

Implantation was completed on April 8, 1981, and good metabolic control was reached immediately and has continued to date (July 1981), with this unit providing the only source of insulin. There have been no hypoglycemic attacks. Patient acceptance is very good. The Siemens unit, PFA 01 (external) and DFA 01 (implanted) has proved reliable and precise. DIABETES 30:1072–1075, December 1981.

METHODS
Device. The insulin infusion device (IID) used for implantation consists of two parts (Figure 1). The externally worn part (Siemens PFA 01), measuring 115 × 77 × 25-mm, and weighing 220 g, has two functions. First, it programs the implanted part of the device by carrier frequency. The patient can choose between 12 different basal rates in the range of 0.2–1.5 U insulin/h, and 12 different extra demand infusion rates between 1 and 15 U/h. After triggering the extra demand for insulin during meals, the infusion rate automatically returns to the basal rate after 1 h. Second, the externally worn part of the device functions as a monitor of the
implanted unit (Siemens DFA 01). It can receive signals which give optical and acoustical information about the actual running rate. A catheter-stop alarm can also be recognized by optical and acoustical signals.

The implanted part of the device has a volume of 94 cm³ and has a weight of 180 g when filled with insulin. Its size is 85 × 60 × 22 mm. The pump, motor, battery, and insulin reservoir are housed in a lightweight titanium capsule that is hermetically sealed. The capacity of the insulin reservoir is 10 ml (U100 insulin). Refilling the reservoir is accomplished by injecting insulin through a self-sealing septum. For safety reasons, the contents of the capsule are under negative pressure. The life expectancy of the battery is at least 1 yr, calculated for a daily insulin requirement of approximately 40 U/day. The electronic circuit can be remotely controlled by the external part of the device. (Technical details will be published separately.) The device was tested using extensive experiments with dogs.8,9

**Insulin.** The implanted device was filled with 10 ml of 100 U/ml neutral porcine insulin (Hoe 21PS) prepared by our insulin research group from Hoechst, Frankfurt, with a special additive to prevent aggregation. This additive is a special surface-active compound consisting of a polypropylene glycol polymer chain to which polyethylene glycol has been attached at both ends.7

**Surgical procedure.** For the peritoneal infusion route, implantation in the left upper abdominal region was chosen. An 8–10-cm pararectal vertical skin incision was made beneath the left ribbow. The outer fascia of the left rectus muscle was cut obliquely, the muscle was split bluntly, and the inner fascia of the rectus abdominis was fixed with two long sutures. The peritoneum was opened between these two sutures by a step wound incision. Through this, the catheter was pushed intraperitoneally 3–5 cm toward the left hypogastrium and fixed on the parietal peritoneum with the two previously placed sutures. A further fixation was done within the inner fascia of the rectus muscle. Using a smooth loop, the catheter was led through the rectus muscle and the outer fascia and fixed there again. The subcutaneous bed for the pump was made in the same manner as for a pacemaker implantation on the fascia of the external oblique abdominal muscle. To facilitate later refilling of the insulin reservoir, a small incision was made in the skin covering the refill septum of the implanted unit to create a tiny identifying scar.

**RESULTS**

The wound at the implantation site healed well. After 4 days, 20 ml of clear fluid was withdrawn from the site by syringe, and healing continued uneventfully. Good metabolic control was immediately established and no source of insulin other than the Siemens device was necessary.

Table 1 shows a comparison of quality of metabolic control for M.K. using various routes of insulin delivery. Although the use of conventional s.c. treatment the adjustment of insulin dose was optimized through the use of self-monitoring equipment, M.K. still suffered hypoglycemic attacks several times a week. No improvement was achieved through s.c. infusion.

Hypoglycemic attacks vanished when using i.v. and i.p. infusions because the patient, being less unstable, could sense the impending onset of an episode and compensate

<table>
<thead>
<tr>
<th>Route</th>
<th>Duration (days)</th>
<th>HBA,</th>
<th>MBG ± SD</th>
<th>BG &lt; 40 mg/dl/wk</th>
<th>Insulin requirement (U/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>s.c. inject. therapy</td>
<td>740</td>
<td>9.6</td>
<td>158 ± 24</td>
<td>2.4</td>
<td>64 ± 19</td>
</tr>
<tr>
<td>i.v.</td>
<td>130</td>
<td>138 ± 28</td>
<td>2.5</td>
<td>60 ± 18</td>
<td></td>
</tr>
<tr>
<td>s.c.</td>
<td>79</td>
<td>149 ± 52</td>
<td>3.2</td>
<td>63 ± 20</td>
<td></td>
</tr>
<tr>
<td>i.m.</td>
<td>48</td>
<td>136 ± 37</td>
<td>3.2</td>
<td>58 ± 20</td>
<td></td>
</tr>
<tr>
<td>i.p. externally worn</td>
<td>186</td>
<td>124 ± 30</td>
<td>1.9</td>
<td>48 ± 10</td>
<td></td>
</tr>
<tr>
<td>i.p. implanted</td>
<td>178*</td>
<td>129 ± 24</td>
<td>1.4</td>
<td>47 ± 11</td>
<td></td>
</tr>
</tbody>
</table>

* Until October 2, 1981.
for it quickly. There was no difference in metabolic control between infusions delivered by the externally worn device and the implanted one when using the i.p. route. However, the safer location of the implanted catheter and the elimination of the risk of infection are definite advantages.

Figure 2 shows the mean of 45 days, i.e., all those in which M.K. made full glucose profiles of eight samples. Despite shifting to three large meals daily, he was still able to maintain stable control. Insulin profiles below the glucose curve are drawn to the same scale.

**DISCUSSION**

Our team has pursued first, the development of an externally worn device (Promedos) and second, the development of a remote-controlled implantable device. (Buchwald et al. had previously completed work in November 1980 on a fully implanted constant basal rate device aimed for use with type II diabetics. In January 1981, Schade and Eaton completed the first implantation of a programmable IID for the treatment of insulin-dependent diabetes mellitus. A major hurdle in the early phase of work with both devices was the unforeseen problem of aggregation of insulin within tubes and in the insulin reservoir. This difficulty has now been overcome.

During trials with external pumps, we studied in detail the risks and benefits of various routes of insulin delivery. Since the s.c. and i.m. routes are unsuitable for implanted devices, we considered only the i.v. and i.p. routes. Although our greatest experience has been using an i.v. infusion, we chose the i.p. route for our implantation model. Using i.p. for control is almost as satisfactory as using i.v. (Table 1), and i.p. has several distinct advantages. There is nearly the same quick response of blood glucose that is typical of i.v., but i.p. has the advantage of using the portal route through the liver. There is no risk of thrombosis and therefore less risk of catheter occlusion. For implantation of the device into the abdominal wall we could draw on the vast body of surgical experience gained from earlier pacemaker implantations.

**Safety features.** In our Siemens device the insulin reservoir is enclosed in a titanium capsule under reduced pressure, protecting it from external penetration, and safely allowing the capacity to be greatly increased.

If failure occurs in the “on” mode, insulin flow can be stopped with a magnet. In the “off” mode, failure may be detected even before blood glucose levels rise when the patient makes a check using the external unit.

As safety features are refined they should become more and more automatic, and less dependent on active monitoring by the patient. One must also realize how dependent further study is on the cooperation and motivation of patients, until such time as a good sensor for blood glucose determination becomes available.

During the more than 180 days of continuous use, our implanted unit has proved to be a reliable and precise insulin-dosing device. We have not experienced a single hypoglycemic attack. There has been only one incident of an unforeseen rise in blood glucose, which proved to be caused by patient error in calculating total insulin consumption, and allowing the reservoir to run dry.

M.K. found that after implantation he could return to a full work load, reduce his number of meals from six to three, and vary time and size of meals while continuing to maintain good control.

When an implanted device is used, one loses the ability to exchange units in a simple manner when a defect occurs or a refinement appears. However, years of experience with pacemaker equipment has provided us with enough technical knowledge to make implantation surgery relatively simple, and it may even be done under local anesthesia.

In this early phase of research, we are well aware of the risks and current deficiencies of implantation, and are not suggesting that it may soon become a routine procedure. Secondary studies aimed at ameliorating existing complications of metabolic imbalance may be feasible when using externally worn devices. The urgent primary studies proving that good metabolic control prevents late complications will only be possible when we have safer, but implantable, devices.

**FIGURE 2.** The mean of 45-day-long profiles of metabolic control, food intake, and insulin use (M.K., April–June 1981).
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REFERENCES