Insulin Therapy during Peritoneal Dialysis: Pros and Cons of Various Forms of Administration

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Abstract. Major fluctuations of blood glucose, hyperinsulinemia, and the formation of insulin antibodies can be prevented by intraperitoneal insulin administration during peritoneal dialysis in patients with diabetic nephropathy. The reduction in insulin requirement is most pronounced compared with subcutaneous administration when insulin is instilled into the empty abdominal cavity. If insulin is instilled into the abdominal cavity along with the dialysis fluid, there are losses of activity due to delayed absorption consequential to dilution by the fluid and adsorption to the plastic surface of the dialysis solution delivery systems. These may be so pronounced as to make intraperitoneal administration uneconomical. The effectiveness of peritoneal dialysis is not affected by intraperitoneal insulin administration. The frequency of peritonitis during intraperitoneal insulin administration increases slightly only in continuous ambulatory peritoneal dialysis, but not in intermittent peritoneal dialysis.

In peritoneal dialysis treatment of patients with diabetic nephropathy, the optimum adjustment of blood glucose values is made more difficult by additional supply of glucose via the peritoneum. As a further difficulty, this occurs discontinuously in intermittent peritoneal dialysis (IPD), in contrast to continuous ambulatory peritoneal dialysis (CAPD). The objective of insulin treatment during peritoneal dialysis is to maintain "euglycemia" during the dwell time, to prevent postprandial hyperglycemia, and to avoid hypoglycemia in the morning. It must be kept in mind that by itself, uremia alters the physiology of insulin response to glucose load.

Materials and Methods
Comparison of the Routes of Insulin Administration

Intraperitoneally administered insulin is absorbed more rapidly and evenly than subcutaneously administered insulin. It passes directly into the portal vein system. From the liver, it influences glucose and lipid metabolism (1). In people without diabetes, the liver metabolizes 50 to 70% of the absorbed insulin. In the basal status, the ratio of portal to peripheral insulin is 3:1 and increases to a maximal value of 9:1 after administering glucose. In peritoneal dialysis with the addition of insulin to the dialysis fluid solution, insulin is absorbed continuously during the entire dwell time. Major fluctuations in blood glucose values occur after subcutaneous insulin administration, caused by different rates of degradation of insulin after leaving subcutaneous tissues, which depend on the depth and position of injection, physical exertion, and regional blood flow. These fluctuations can be minimized with intraperitoneal administration.

Animal experiments show that only the route via the portal system enables plasma levels of the hormone and its metabolites to approximate those found in normal subjects. Lindblad et al. (2) presented a compilation concerning the treatment of diabetes in 499 CAPD patients of the US National Institutes of Health CAPD Registry. Eighty-six percent of the patients had been treated with insulin, 6% by diet, 4% with oral hypoglycemic agents, and 2% with insulin plus oral hypoglycemic agents; 2% received no therapy. Of the 86% of the patients treated with insulin, as many as 54% had been given this hormone intraperitoneally, 36% subcutaneously, and 10% via the combined subcutaneous and intraperitoneal routes.

Intraperitoneal insulin administration can selectively inhibit the excessively high hepatic glucose release in people with diabetes who do not require insulin administration. The degree of hyperinsulinemia is less than with subcutaneous administration. At a given dose of insulin, the amount reaching the periphery is much less in intraperitoneal than in subcutaneous administration. This is especially important because the circulating insulin is directly correlated with the risk of arteriosclerosis. Some studies (3–5) show that intraperitoneal administration of insulin leads to lipoprotein profiles with a lower atherogenic potential. Moreover, it could be demonstrated in glucose clamp experiments that the insulin-dependent uptake during CAPD is nearly normal with intraperitoneal administration of insulin, compared with the situation in hemodialysis patients with subcutaneous insulin administration (6). Although the pathophysiologic considerations support general administration of insulin via the intraperitoneal route, there are problems in the practical implementation that prejudice the value of such a measure (7). Below, I present the advantages and disadvantages of these routes of administration by reference to the literature and to my own observations and investigations.

Insulin Requirement with Various Modalities of Treatment

The insulin requirement per day was determined in 16 hemodialysis patients, 18 hemofiltration patients, 26 CAPD patients, and 14 IPD patients at the onset of diabetes mellitus, at the start of artificial kidney treatment, and 18 mo after the beginning of therapy. It should be emphasized that these patients, as all others being investigated, had type 1 diabetes. Twelve of the 26 CAPD patients were given the insulin subcutaneously and 14 intraperitoneally via the tube system.
Six of the 14 IPD patients received the insulin subcutaneously and 8 intraperitoneally.

**Statistical Analyses**

Data are expressed as means ± SD. Statistics were performed by the Wilcoxon test for comparison of paired samples and the Mann-Whitney test for comparison of unpaired samples. Differences were considered to be statistically significant at $P < 0.05$.

**Results**

**Changes in Insulin Requirement during the Course of Renal Failure**

The results of this investigation are shown in Figure 1. In the patients of all groups, the insulin requirement at the beginning of dialysis treatment had fallen significantly to about half compared with the dose at the diagnosis of diabetes mellitus. A further, less substantial reduction of insulin requirement was observed in the hemodialysis group and the hemofiltration patients after 18 mo of treatment. In CAPD and IPD, this reduction only occurred when insulin was administered subcutaneously. The insulin requirement rose to the initial range or above in both CAPD and IPD patients when the insulin had been given intraperitoneally—that is, via the tube system with the inflowing dialysis fluid. The raised insulin requirement in intraperitoneal administration during CAPD and IPD is explained by the effect of dilution and by the adsorption and thus inactivation by plastic surfaces (in this case, tubings and dialysis fluid bags).

**Adsorption of Insulin to Surfaces**

The adsorption of insulin to the polyvinyl chloride surfaces of dialysis fluid bags and tubings was investigated in detail by Johnson *et al.* (8) and by Wideröe *et al.* (9). The two groups arrived at different results. Johnson *et al.* (8) could detect approximately 10% binding of insulin to the polyvinyl chloride reservoirs after the first minute and approximately 20% after 15 min. The amount of insulin adsorbed correlated directly

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*Figure 1. Mean insulin requirement per day in 16 hemodialysis, 18 hemofiltration, 26 continuous ambulatory peritoneal dialysis (CAPD), and 14 intermittent peritoneal dialysis (IPD) patients at onset of diabetes mellitus (green bars), at the commencement of dialysis therapy (yellow bars), and after 18 mo of dialysis treatment (gray bars). HD, hemodialysis; HF, postdilutional hemofiltration. Route of administration: ip, intraperitoneal with the dialysis fluid; sc, subcutaneous.*
with the surface area of the reservoir and inversely with the concentration of insulin in the dialysis fluid. On the other hand, Wideroe et al. (9) found unfavorable results when they used radiolabeled $^{125}$I insulin. They measured 65% retention of the insulin injected into the reservoir, and only 35% passed into the abdominal cavity.

Figure 2 shows the insulin requirement in relation to the route of administration and the dialysis modality in the patients in this study. Groups of 12 patients each were investigated; I assessed whether the insulin requirement was affected by administering the insulin either into the empty abdominal cavity or into the abdominal cavity along with the dialysis solution. It was shown that in CAPD, and to an insignificant extent also in IPD, the insulin requirement was less if insulin was administered into the empty abdominal cavity (i.e., before instilling dialysis fluid). The requirement rose when the insulin was infused with the dialysis fluid into the abdominal cavity, especially in CAPD. Because the amount of glucose administered in CAPD and IPD was identical, differences in insulin adsorption by plastic must be considered as a potential explanation for the different insulin requirements between CAPD and IPD. These findings indicate that the insulin should be administered if possible into the empty abdominal cavity (i.e., before instillation of the dialyzing solution) in intraperitoneal administration, especially in CAPD.

**Glucose Control with Intraperitoneal Insulin**

Figure 3 shows a more favorable effect on glucose control with intraperitoneal administration of insulin in CAPD. The insulin was instilled directly into the empty abdominal cavity before administering the dialysis fluid. Whereas the insulin requirement was 62 U/24 h in subcutaneous administration, it was merely 40 U/24 h with intraperitoneal administration. Short-acting insulin was provided in both cases. The blood glucose values fluctuated less with intraperitoneal administration of insulin than with subcutaneous administration.

**Glucose Absorption in CAPD and IPD**

The glucose absorption in CAPD can be calculated in accordance with the formula of Grodstein et al. (10):

$$GU = [11.3 \times (G - 10.9)] \times V$$

where GU is the glucose uptake, G the mean glucose concentration in the dialysis fluid, and V is the volume of dialysis fluid. Because of the differences of dialysis fluid administration periods between CAPD and IPD, glucose absorption was calculated in relation to the glucose concentration instead of the period of time.

Figure 4 shows the glucose absorption from dialysis fluid in relation to the glucose concentration in the fluid and the administration mode of insulin in 20 patients with diabetic nephropathy. Ten of these patients were treated with CAPD, whereas the other 10 were treated with IPD. There was no statistically significant difference between intraperitoneal and subcutaneous administration of insulin at a glucose concentration of the dialysis fluid of 13.6 g/L. At higher concentrations, however, there was a markedly higher glucose absorption when insulin was added to the dialysis fluid than with subcutaneous application.

These findings indicate that the intraperitoneal administration of insulin leads to more even glucose levels, but that when dialysis fluids with glucose concentrations higher than 13.6 g/L are used, the absorption of glucose from the abdominal cavity is greater both in CAPD and in IPD with intraperitoneal insulin treatment than it is with subcutaneous administration. The raised glucose absorption from the abdominal cavity in intraperitoneal insulin administration must be regarded as a disadvantage of this route of application in view of the problems present, in particular in patients with type 2 diabetic nephropathy.
Absorption of insulin from dialyzing solution instilled in the abdominal cavity in three CAPD patients with diabetic nephropathy was compared with that in three CAPD patients without diabetes by Wideröe et al. (9). After a dwell time of 30 min, the absorption of insulin from the abdominal cavity in the patients with diabetes was much higher than in the patients without diabetes, which the authors interpreted as the result of receptor interaction.

Optimization of Blood Glucose by Intraperitoneal Insulin

I investigated the quality of glucose control with intraperitoneal and subcutaneous insulin administration in 15 patients with diabetic nephropathy who were undergoing CAPD treatment. The patients initially injected the insulin subcutaneously during 3 mo. Afterward, they were asked to instill the insulin (dissolved in 100 ml physiologic saline) into the abdominal cavity before the instillation of dialysis fluid. To ensure that all of the insulin passed into the abdominal cavity, 100 ml of physiologic saline was injected after it. After each treatment period, hemoglobin (Hb) A1c was determined. Under the conditions described, the dose of insulin was reduced by approximately 20% in intraperitoneal as compared with subcutaneous administration. The HbA1c level was in a much more favorable range (6.1 ± 1.2%) in intraperitoneal insulin administration than with subcutaneous insulin administration (8.4 ± 1.3%). However, a disadvantage of the method described is an increased time requirement for direct instillation of insulin into the abdominal cavity. The results confirm the findings of Stephen et al. (11), who were able to observe a fall of HbA1c from an average of 10.6 to 8.3% after switching from subcutaneous to intraperitoneal insulin administration.

Effect of the Route of Administration on Lipids

Serum total cholesterol, HDL, LDL, and triglycerides were measured at the end of each 6-mo period in which insulin had been administered either subcutaneously or intraperitoneally in 10 CAPD patients with diabetic nephropathy. As shown by Table 1, the parameters measured did not show any significant differences apart from LDL cholesterol. The LDL cholesterol fell to a statistically significant extent with intraperitoneal insulin administration into the empty abdominal cavity. An explanation for this phenomenon is not readily available; further investigations are required.

Dialysis Efficacy and Complications

The weekly clearance of creatinine is a measure for the effectiveness of peritoneal dialysis. It was determined in 10 CAPD and 8 IPD patients before and after switching from subcutaneous to intraperitoneal administration of insulin after an average of 15 mo had elapsed. There was no significant change in the weekly creatinine clearance in either CAPD or IPD after the switch (Table 2). Accordingly, the efficiency of dialysis is not affected by the route of insulin administration.

The incidence of peritonitis was of particular interest, especially because there was a concern that microorganisms would pass into the abdominal cavity with the additional manipulation associated with intraperitoneal insulin administration. The incidence of peritonitis in patients both with and without diabetes in CAPD and IPD is shown in Table 3. The patients with diabetes were subdivided into those who used subcutaneous and those who used intraperitoneal insulin administration. As expected, peritonitis occurred more rarely in people without diabetes during IPD than during CAPD treatment. The incidences were 1 event per 36.4 treatment months for IPD and 1 event per 28.6 treatment months for CAPD. In patients with diabetes, the risk of peritonitis increased with intraperitoneal insulin administration in both IPD and CAPD. However, the results reached a level of statistical significance of \( P < 0.05 \) only in CAPD.

Figure 5 presents the percentage of patients who were free of peritonitis during the course of a 24-mo CAPD treatment with subcutaneous or intraperitoneal insulin administration. This investigation comprised 24 patients in whom the insulin was injected subcutaneously and 12 in whom the administration was intraperitoneal. There were no statistically significant differences between the two groups.

Conclusion

The advantages of intraperitoneal insulin administration include a more physiologic effect of insulin in patients with

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Subcutaneous</th>
<th>Intraperitoneal</th>
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<tbody>
<tr>
<td>Cholesterol (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>257 ± 12</td>
<td>239 ± 17</td>
</tr>
<tr>
<td>HDL</td>
<td>36 ± 8</td>
<td>41 ± 16</td>
</tr>
<tr>
<td>LDL</td>
<td>181 ± 15&lt;sup&gt;a&lt;/sup&gt;</td>
<td>141 ± 18</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>374 ± 27</td>
<td>381 ± 32</td>
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<sup>a</sup> \( P < 0.001 \) versus intraperitoneally administered insulin.
Table 2. Weekly peritoneal creatinine clearance before and after switching to intraperitoneal insulin administration

<table>
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<tr>
<th>Time</th>
<th>CAPD</th>
<th>IPD</th>
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<tbody>
<tr>
<td>Before switching</td>
<td>54.6 ± 8.1</td>
<td>49.6 ± 10.4</td>
</tr>
<tr>
<td>After switching</td>
<td>55.8 ± 7.9</td>
<td>48.6 ± 9.6</td>
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On average, intraperitoneally administered insulin was provided for 15 mo. CAPD, continuous ambulatory peritoneal dialysis; IPD, intermittent peritoneal dialysis.

Table 3. Incidence of peritonitis in patients with and without diabetes

<table>
<thead>
<tr>
<th>Diabetes Status</th>
<th>CAPD</th>
<th>IPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients without diabetes</td>
<td>1:28.6</td>
<td>1:36.4</td>
</tr>
</tbody>
</table>
| Patients with diabetes
| sc insulin      | 1:32.9 | 1:39.5 |
| ip insulin      | 1:26.4 | 1:38.9 |

Numbers are presented in patient-months. CAPD, continuous ambulatory peritoneal dialysis; IPD, intermittent peritoneal dialysis; sc, subcutaneous administration; ip, intraperitoneal administration.

Figure 5. Number of continuous ambulatory peritoneal dialysis (CAPD) patients who remained free of peritonitis during the course of 2 yr who were treated with subcutaneously (sc; solid circles) or intraperitoneally (ip; open circles) administered insulin.

Disadvantages include a raised insulin requirement in intraperitoneal insulin administration, which is based on the dilution effect and in particular on insulin binding to the plastic surface of the dialysis fluid reservoir. This disadvantage can be eliminated in part by instilling the insulin into the empty abdominal cavity. However, this requires in more elaborate manipulation. If the insulin is instilled into the abdominal cavity along with the dialysis solution, switching from subcutaneous to intraperitoneal administration entails an increase of the insulin requirement by approximately 30%. However, the resulting increased costs are compensated by the advantage of optimized adjustment of blood glucose levels. As expected, the rate of peritonitis in intraperitoneal insulin administration is mainly increased in CAPD. However, it is still in an acceptable range compared with patients without diabetes.

References
5. Pyorala K: Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: Results from two population studies in Finland. *Diabetes Care* 131: 141, 1973