The treatment of diabetic end-stage renal disease with peritoneal dialysis

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Introduction

Since the introduction of continuous ambulatory peritoneal dialysis (CAPD) to clinical practice, this modality of end-stage renal disease treatment has appeared as an appealing dialysis procedure for patients with insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) diabetes mellitus. Furthermore, since the early 1980s, patients’ survival has been so encouraging that CAPD has become the preferred mode of therapy for diabetic patients [1,2]. In addition, some proposed benefits have been taken into account when choosing CAPD for diabetic patients: the slow and sustained ultrafiltration associated with a relative lack of rapid fluid and electrolyte changes compared with haemodialysis; the preservation of residual renal function for a longer period than haemodialysis; the possibility of the intraperitoneal route for insulin administration; an easier control of blood pressure; an easier access for dialytic procedure; and the stability of biochemical parameters [3].

Despite these attractive advantages, some drawbacks of CAPD have raised a few concerns regarding the widespread application of this dialytic modality to the diabetic population. Infections are common features of peritoneal dialysis and, since diabetic patients have a more pronounced immunodepression, they are likely to develop a rather more severe infection. Continuous loss of protein through the dialysate may aggravate a nutritional problem. The most important concern is the continuous absorption of glucose from the dialysis fluid: this process could be responsible for excessive weight gain, hyperlipidaemia and accelerated atherosclerosis [3].

During 20 years of peritoneal dialysis history, advances in the field, clinical experience and extensive studies have enabled us to address some of these concerns. Some conflicting issues are still under debate regarding the improved approach to the diabetic patient. These issues could be summarized in terms of a few questions: (i) are infections a major problem?; (ii) is intraperitoneal insulin administration more convenient than the subcutaneous route?; (iii) is there any benefit to using alternative non-glucose osmotic agents?; and (iv) is peritoneal dialysis the preferred modality in diabetic patients?

Infections

Peritonitis is one of the major causes of morbidity in CAPD patients. Despite the early fear that diabetic patients would have a greater peritonitis rate with atypical bacteria than non-diabetic patients, analysis of large populations indicated that frequency, clinical manifestations and management of peritonitis in diabetic and non-diabetic patients are similar [4–6]. It is important to remember that almost all patients used to be treated with the old connection systems and the peritonitis rate was high (1 per 6.2 patient/months in diabetic and 1 per 5.3 in non-diabetics patients) [5]. No differences in catheter-related infections between the two groups were reported [7,8].

In more recent years, a large single centre prospective study showed that the peritonitis rate was significantly greater in the diabetic group (1.2 vs 0.8 episodes/patient/year), despite the fact that no difference was found in the time from the first episode of infection in diabetics and non-diabetics [9]. All patients used the ultraviolet germicidal exchange device for bag connections. As regards exit site infection, despite some studies [6] which showed an increased rate of exit site infection in diabetic patients, a more recent and prospective analysis did not find any difference between diabetic and non-diabetic patients in the first episode in terms of catheter-related infection and exit site infection [9].

Published data on the severity of CAPD peritonitis in diabetic patients is scanty. Traneus et al. [10] reported an increased frequency of complications of
CAPD peritonitis in diabetic patients. In this study, 82% of the peritonitis in diabetic patients required hospital treatment, whilst only 53% of non-diabetic patients with peritonitis were admitted to hospital. In addition, diabetic patients developed recurrence and a protracted course more frequently (44%) than non-diabetic patients (15%). This difference was statistically significant.

In contrast to these results, Tzamaloukas et al. [11] recorded no difference between diabetic and non-diabetic patients with regard to the persistence of peritonitis for 5 days or more and relapse of peritonitis within 30 days. In this study, the peritonitis rate was 1/14.3 patient months for diabetic and 1/14.8 for non-diabetic patients; also the percentage of peritoneal catheter removal for peritonitis was no different in the two groups.

However, a higher death rate in diabetic patients due to peritonitis episodes was recorded and attributed to an increased cardiovascular mortality in NIDDM patients because of severe malnutrition during or just after occurrence of the peritonitis. A negative correlation between serum albumin concentration and the myocardial infarction rate in NIDDM patients on chronic dialysis was found.

**Intraperitoneal insulin administration**

There is evidence to suggest that intraperitoneal (i.p.) insulin delivery allows faster and consistent absorption of insulin. There are several similarities between the absorption kinetics of intraperitoneally administered insulin and the normal secretion of insulin by islet cells. Therefore, when CAPD was first introduced, peritoneal dialysis in diabetic patients was defined as the ‘artificial pancreas’ [12]. In physiological conditions, insulin is secreted by islet cells and taken into the portal vein. Thereafter, the liver removes 50–60% of the secreted insulin [13]. Insulin administered into the peritoneal cavity is absorbed by diffusion across the visceral peritoneum into the portal venous circulation. Additionally, direct absorption through the capsule of the liver has also been reported [14].

Thus, in this way, i.p. insulin is not delivered directly into the circulation, and maintains the physiological insulin portal/peripheral ratio of ~ 3:1; consequently, the systemic circulation is exposed to a much lower concentration of this hormone [15]. This is likely to be advantageous, since systemic hyperinsulinaemia has been linked to acceleration of atherosclerosis.

With the peripheral route of insulin delivery, euglycaemia is achieved at the expense of peripheral hyperinsulinaemia, and possibly results in increased hepatic glucose production. Insulin delivered by the i.p. route works directly to reduce hepatic glucose output. Some clinical experience indicates that peritoneal insulin delivery is associated with an improved control of blood glucose. This leads to fewer glycaemic episodes, hence the differences between daily maximum and minimum glucose values are lower compared with subcutaneous insulin. Moreover, the frequency of hypoglycaemia episodes is reduced with peritoneal insulin [13].

Some studies suggested that i.p. insulin therapy is associated with lipoprotein profiles of lower atherogenic potential [3], a reduction in the cholesterol content of high density lipoproteins (HDLs) with no change in apolipoproteins A-1 and A-2. Additionally, i.p. administration was associated with very low density lipoprotein (VLDL) triglycerides, VLDL apolipoprotein B and near normal levels of cholesterol ester transfer. The conclusion of these studies was that i.p. insulin was more physiological and corrected a key step in the reverse cholesterol transport in IDDM patients.

A recent study [16], however, presented data which contrasted with the previous studies. In a cross-over setting, HDL cholesterol significantly decreased during i.p. treatment, and the LDL/HDL cholesterol ratio was higher. Total cholesterol, LDL cholesterol and triglycerides were again higher during i.p. insulin administration. The conclusions of this study were that although i.p. insulin offers significantly better glycaemic control and insulin sensitivity than subcutaneous insulin, the effect on serum lipids is more disadvantageous.

Some concerns were raised about the frequency of peritonitis in patients undergoing i.p. insulin treatment. Despite the fact that the national CAPD registry survey of peritonitis revealed that i.p. insulin administration was not associated with an increased risk of peritonitis [17], two European studies demonstrated an increased frequency [18,19]. Selgas et al. [19] recorded an incidence of peritonitis four times greater in the i.p. group as compared with the subcutaneous insulin group (1/14.4 patient months in the i.p. group and 1/62.4 patient months in the subcutaneous group).

Another problem was the association between i.p. insulin and subcapsular liver steatosis. Wanless et al. [20] described a unique form of hepatic steatosis in which hepatic triglyceride deposition was confined to the subcapsular region of the liver. This finding was seen only on autopsy examination and was not associated with hepatic abnormalities ante-mortem. All cases were diabetic patients on peritoneal dialysis in whom insulin was administered by the i.p. route.

It was suggested that the insulin and glucose in the dialysate fluid bathing the surface of the liver diffuse across the hepatic capsule. The concentration of insulin and glucose is very high only in the first few layers of hepatocytes and, in this region, free fatty acids are esterified preferentially and lipoprotein production may be suppressed. These conditions greatly favour the steatotic process.

**Alternative osmotic agents**

On average, a CAPD patient typically absorbs 100–150 g of glucose daily during treatment. Apart from the increased caloric load, in diabetic patients a
higher dose of insulin is required to maintain blood glucose control. Every new osmotic agent proposed as an alternative to glucose has claimed to be advantageous in diabetics. However, few specific studies have been published about alternative osmotic agents in diabetic patients.

A glycerol-containing dialysis solution was well tolerated by diabetic patients and its use was associated with an initial decreased requirement for insulin; however, this favourable effect was not maintained after 3–4 months [21]. Better control of glucose homeostasis and an improved survival rate were reported in these patients [22]. The use of a glycerol-containing solution inevitably leads to an accumulation of glycerol in the blood, and these high levels were associated with hyperosmolar symptoms in a few cases [23]. Long-term studies have shown a dramatic increase in the blood fasting triglyceride concentration after 6 months of treatment. However, this finding was due mainly to a methodological problem.

Recent studies have proposed the use of a combination of glycerol and amino acids in the peritoneal dialysis fluid [24]. By using this composite, the concentration of both substances is reduced, thus decreasing the side effects of both. The major advantage of the amino acid–glycerol solution is the reduction in carbohydrate absorption and the independence from insulin for metabolism. A long-term study in the rat and experience in patients showed that the solution can be used safely [24].

An amino acid-containing solution could present some advantages for the diabetic population as compared with the standard glucose solution, mainly because patients use one exchange per day less than glucose-containing solution. Few data have been published on this issue: the longest study available with the 1% amino acid solution describes four diabetic patients followed-up for >12 months [25]. Serum albumin and cholesterol increased as compared with a control group.

High molecular weight Icodextrin appears to be a safe and effective osmotic agent, providing sustained ultrafiltration. No specific studies so far have been performed in diabetic patients, even in large multicentre investigations [26].

Patients and technique survival

During the early years of CAPD, encouraging results on patients’ survival indicated CAPD as the preferred mode of therapy for diabetic patients. Subsequently, large databases have shown discordant results. A historical US prospective sample of 1725 diabetic and 2411 non-diabetic Medicare end-stage renal disease patients from 1986 to 1987 demonstrated that the mortality risk was not statistically different between CAPD and haemodialysis groups for non-diabetic patients, while evidence of a higher adjusted mortality for CAPD compared with haemodialysis was found amongst diabetic patients [27]. These data were confirmed by the USRDS 1994 report [28]. In this large database, the death rate of diabetic haemodialysis patients was lower than that of peritoneal dialysis patients for every subset grouped by age.

In these large registries, however, the dialysis dose delivered was not taken into account. A recent analysis comparing two large databases (the CANUSA study for peritoneal dialysis and the RKDP, Minneapolis HD data base for haemodialysis) was performed [29]. Diabetic patients were divided into three age groups and two levels of Kt/V. The results of 2 year patient survival are shown in Table 1. These results demonstrate that comparable survival is achieved in haemodialysis and peritoneal dialysis as long as the therapy dose is matched. A large Italian regional registry (in Lombardia) confirmed these findings [30]. The relative death risk in patients on peritoneal dialysis vs those on haemodialysis, after taking into account the main co-morbid conditions, did not differ significantly, as estimated by the Cox proportional hazards regression model. Five year survival of diabetic patients was 34%, and no differences were found between haemo- and peritoneal dialysis in terms of mortality. Our 10 year experience fully confirmed these data (Figure 1).

Conclusions

From 20 years of experience of CAPD, it appears that peritoneal dialysis is a viable treatment option for a diabetic patient with end-stage renal disease. The benet

<p>| Table 1. Two year survival on haemodialysis (HD) and CAPD in relation to dialysis dose and age |
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<table>
<thead>
<tr>
<th>HD Kt/V 1.0–1.5</th>
<th>CAPD Kt/V 1.7–2.1</th>
<th>HD Kt/V &gt;1.5</th>
<th>CAPD Kt/V &gt;2.1</th>
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<tr>
<td>&gt;61 years</td>
<td>56 ±4</td>
<td>64 ±8</td>
<td>74 ±3</td>
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<tr>
<td>46–60 years</td>
<td>70 ±4</td>
<td>79 ±6</td>
<td>83 ±3</td>
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<tr>
<td>&lt;45 years</td>
<td>87 ±3</td>
<td>87 ±5</td>
<td>93 ±2</td>
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Fig. 1. Three year survival of diabetic end-stage renal disease patients treated with peritoneal dialysis in our centre (1990–1996).
fit of i.p. treatment with insulin is reduced by the higher incidence of peritonitis episodes. On the contrary, peritonitis, the main concern of CAPD treatment, does not seem to be a particular problem for diabetics not treated with i.p. insulin. Data on survival do not confirm the superior effect of CAPD compared with haemodialysis, as suggested in the early years of CAPD.

References


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