A Patient on Peritoneal Dialysis with Refractory Volume Overload

Martin Wilkie

Abstract
The management of volume in patients with diabetes on peritoneal dialysis is affected by several factors, including the degree of residual renal function, peritoneal membrane small-solute transport, salt and water intake, blood sugar control, comorbidity, and nutritional status. It requires sequential evaluation of volume status and adjustment of the peritoneal dialysis prescription on the basis of assessments of membrane function and alterations in urine volume. Steps should be taken to preserve residual renal function for as long as possible. Ultimately, in patients who have become anuric and have developed ultrafiltration failure, timely transfer to hemodialysis may be necessary, requiring discussion and planning with the patient.


Introduction
A 66-year-old woman with insulin-dependent diabetes mellitus has CKD secondary to diabetic nephropathy. Her comorbidities include poorly controlled hypertension, proliferative retinopathy, peripheral and autonomic neuropathy (episodic postural hypotension), and paroxysmal atrial fibrillation. She is intolerant of several antihypertensive medications and has been reluctant to increase doses. By August of 2009, she had symptomatic uremia and commenced three times weekly in-center hemodialysis (HD) through a tunneled right internal jugular line. A left brachial arteriovenous fistula (AVF) was fashioned that same month. A coronary angiogram in March of 2010 showed mild coronary artery disease, and her name was placed on the deceased donor transplant waiting list. She became unhappy on HD and transferred to peritoneal dialysis (PD) toward the end of 2010.

Initial PD Treatment
Her initial prescription was 4×2-L exchanges of a 1.36% glucose lactate–buffered dialysate solution (Baxter Dianeal) overnight using automated peritoneal dialysis (APD) with 500 ml same solution for the daytime dwell. However, when she was reviewed in the clinic, she complained that the dialysate volume used for the overnight dialysis was uncomfortable, and therefore, the fill volume was reduced to 1.5 L. She was trained to use mupirocin cream as part of her exit site care. By March of 2011, she was requiring use of occasional 2.27% glucose dialysate bags to maintain fluid balance, despite a urine output of nearly 1 L (Tables 1 and 2). A peritoneal equilibration test (PET) using 2.27% glucose showed a 4-hour dialysate/plasma (D/P) creatinine ratio of 0.95 and negative ultrafiltration (UF) of −40 ml, which indicated that she was a fast transporter (Table 1). She experienced some difficulty with catheter flow manifested by drainage alarms on APD, leading to the introduction of an 80% tidal prescription. A tidal prescription is where the minimum required drain volume is set at <100% of the fill volume, although for safety reasons, a complete drain is scheduled in the middle and at the end of therapy. This approach is commonly used when impaired PD catheter function leads to drainage alarms. A 1.1% amino acid dialysate bag was included as part of the overnight prescription to reduce overall dialysate glucose exposure.

Incipient Volume Overload
In July of 2011, she had a cough that was considered to be caused by a possible chest infection or a degree of fluid overload. The chest radiograph showed an enlarged heart, generally congested lung fields with patchy air space shadowing at the bases, and small effusions. Her BP control had become more problematic, with a systolic BP up to 160 mmHg. She was, therefore, educated regarding a 1-L fluid restriction and moderate salt restriction (<5 g salt per day). Her PD prescription was adjusted by increasing the dialysate glucose concentration overnight to a mixture of 1.36% and 2.27% glucose and altering her overnight exchange number from four to five over a 9-hour period. Her ramipril dose was increased to 7.5 mg daily, and insulin was adjusted to improve blood glucose control. To enhance UF, 700 ml icodextrin was added as a daytime exchange (the infused volume being limited, because she complained of abdominal bloating). The total UF that she obtained from her PD was about 700 ml/24 h in addition to a continued urine output of just under 1 L. However, she had persistent edema, leading to discontinuation of amlodipine and a recommendation to lower her target weight by 1–2 kg. Methyl dopa was initiated to improve BP control. Small-solute clearance as measured by Kt/V urea and creatinine clearance was

Sheffield Kidney Institute, Sheffield Teaching Hospital National Health Service Foundation Trust, Sheffield, United Kingdom; and Academic Unit of Nephrology, Department of Infection and Immunity, University of Sheffield, Sheffield, United Kingdom

Correspondence:
Dr. Martin Wilkie, Sheffield Kidney Institute, Sheffield Teaching Hospital National Health Service Foundation Trust, Herries Road, Sheffield S5 7AU, UK. Email: martin.wilkie@sth.nhs.uk
adequate, and her serum albumin was in the normal range (Table 2).

Progressive Loss of Residual Renal Function

In July of 2013, she required PD catheter removal because of a *Pseudomonas* exit site infection. After several months on HD using the brachial AVF, she recommenced PD in October of 2013 through a new PD catheter. She experienced an episode of coagulase negative *Staphylococcus* peritonitis in January of 2014 that responded to antibiotic treatment. When reviewed in clinic in April of 2014, her BP was still poorly controlled, with the systolic BP commonly in the region of 150 mmHg. Small-solute clearance had become borderline because of a decline in residual renal function (RRF), and serum albumin had fallen to 29 g/L (Table 2). The PD prescription was 9 hours overnight using five cycles of 1.5 L of a combination of 1.36% and 2.27% glucose at 80% tidal with a daytime icodextrin exchange of 1.2 L. To increase her clearance prescription, an additional evening exchange of 1.5 L 1.36% glucose dialysate was added. She found the extra exchange to be intrusive and therefore, increased the overnight volumes to 1.8 L instead. Her chest x-ray continued to show appearances in keeping with a degree of cardiac failure, including a moderate left and a small right pleural effusion with prominence of upper lobe vessels.

During July of 2014, she experienced an episode of gastroenteritis associated with eating a crab sandwich that resulted in dehydration and hypotension. She subsequently developed atorvastatin-induced myositis that resulted in significant mobility problems and required protracted rehabilitation. The transthoracic echocardiogram showed moderate left ventricular impairment and reasonable right ventricular systolic function. The next month, she reported a reasonable appetite and was rehabilitating gradually, although she found walking difficult and painful and had edema to the knees bilaterally. She was obtaining about 500 ml UF from her APD machine overnight with an additional 300 ml from the daytime icodextrin bag, but her urine output had declined to about 300 ml/d. After some discussion, she reluctantly agreed to undertake a weekly HD session using her existing AVF to remove additional fluid. When reviewed several months later, she had no ankle edema and was removing approximately 3 L fluid at each weekly HD session. Her urine output was minimal at this stage. Her PD prescription was a combination of 2.27% and 1.36% glucose dialysate overnight, from which she ultrafiltrated approximately 500 ml, and 1.2 L icodextrin for the daytime dwell, from which she obtained about 200 ml. She was very reluctant to continue on weekly HD, because she had experienced bruising of the AVF and severe cramps.

Case Discussion

This patient illustrates a number of features that are central to the understanding of the effective delivery of PD. Although the patient’s small-solute clearance values were adequate throughout, she had a recurrent tendency to volume overload from the beginning of her treatment with PD. This was initially despite a good residual urine volume of approximately 1 L/24 h, but it became more problematic after the urine volume declined. Although urine volume commonly declines with time on PD, contributory factors in this patient included exposure to HD after the removal of the PD catheter for a *Pseudomonas* exit site infection, an episode of peritonitis, and an episode of gastroenteritis, which was associated with hypovolemia.

An important risk factor for volume overload was that she was a fast transporter throughout, which is illustrated in Table 1, and had consistently low UF capacity. The principal strategies to manage this problem included cycling

<table>
<thead>
<tr>
<th>Date</th>
<th>4-h D/P Creatinine</th>
<th>Volume In (ml)</th>
<th>Volume Out (ml)</th>
<th>Net UF (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>February 2011</td>
<td>0.95</td>
<td>2000</td>
<td>1960</td>
<td>−40</td>
</tr>
<tr>
<td>August 2011</td>
<td>0.65</td>
<td>2000</td>
<td>2250</td>
<td>250</td>
</tr>
<tr>
<td>April 2012</td>
<td>0.74</td>
<td>2000</td>
<td>2000</td>
<td>0</td>
</tr>
<tr>
<td>May 2014</td>
<td>0.87</td>
<td>1500</td>
<td>1450</td>
<td>−50</td>
</tr>
</tbody>
</table>

D/P, dialysate/plasma; UF, ultrafiltration.

<table>
<thead>
<tr>
<th>Date</th>
<th>Serum Albumin (g/L)</th>
<th>Net UF (ml)</th>
<th>Urine volume (ml)</th>
<th>Kt/V P</th>
<th>Kt/V U</th>
<th>Kt/V Total</th>
<th>CCI P (L/wk)</th>
<th>CCI U (L/wk)</th>
<th>CCI (total L/wk)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 11</td>
<td>27.0</td>
<td>1097</td>
<td>945</td>
<td>1.75</td>
<td>0.92</td>
<td>2.67</td>
<td>39.1</td>
<td>38.6</td>
<td>78.4</td>
<td>64.0 (BMI=25)</td>
</tr>
<tr>
<td>July 11</td>
<td>38.0</td>
<td>351</td>
<td>930</td>
<td>1.63</td>
<td>0.79</td>
<td>2.42</td>
<td>37.0</td>
<td>31.9</td>
<td>68.9</td>
<td>66.0</td>
</tr>
<tr>
<td>February 12</td>
<td>34.0</td>
<td>527</td>
<td>811</td>
<td>1.54</td>
<td>0.57</td>
<td>2.11</td>
<td>33.3</td>
<td>23.7</td>
<td>57.0</td>
<td>66.0</td>
</tr>
<tr>
<td>August 12</td>
<td>35.0</td>
<td>345</td>
<td>862</td>
<td>1.43</td>
<td>0.57</td>
<td>2.00</td>
<td>31.8</td>
<td>23.5</td>
<td>55.3</td>
<td>65.0</td>
</tr>
<tr>
<td>April 14</td>
<td>29.0</td>
<td>534</td>
<td>461</td>
<td>1.51</td>
<td>0.24</td>
<td>1.75</td>
<td>40.31</td>
<td>9.33</td>
<td>49.6</td>
<td>70.0</td>
</tr>
<tr>
<td>December 14</td>
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<td>1135</td>
<td>517</td>
<td>1.67</td>
<td>0.21</td>
<td>1.88</td>
<td>37.8</td>
<td>21.4</td>
<td>59.2</td>
<td>67.0</td>
</tr>
</tbody>
</table>

UF, ultrafiltration; P, peritoneal; U, urinary; CCI, creatinine clearance; BMI, body mass index.
PD (APD) and the use of icodextrin. It was important to ensure that the prescription was adjusted to avoid the re-absorption of fluid from any exchanges by shortening the dialysate dwell time through the use of cycling PD. Dialysate glucose was increased to augment UF; however, this was done cautiously because of concerns regarding glucose exposure. A key component of the prescription was the use of an icodextrin exchange during the day. Icodextrin provides sustained UF over a longer dwell, despite the fast transport status, because it makes use of the effectively increased peritoneal surface area in this patient population. Poor catheter function affects drain volumes, and in this patient, an 80% tidal prescription was required to prevent drainage alarms. This resulted in an increased residual peritoneal volume at the end of the drain, resulting in a modest dilution of the dialysate glucose concentration and slightly reduced UF.

**RRF**

Most registry studies indicate an overall survival benefit with the use of PD over HD for the first 2 years of dialysis (1), presumably while RRF persists. However, this beneficial effect has consistently not been shown for older women with diabetes (2). The importance of the effect of RRF on outcome among patients on PD was first clarified from a reanalysis of data from the Canada-USA Study, from which it became clear that peritoneal was not equivalent to renal clearance (3). A range of factors affect RRF, and these include prior HD, female gender, higher comorbidity, proteinuria, baseline residual GFR, dialysate glucose exposure, and number of peritonitis episodes. In addition, there are several modifiable factors that can potentially affect RRF, including the use of angiotensin-converting enzyme inhibitors or receptor blockers, diuretics, volume status, the use of aminoglycosides to treat peritonitis, and contrast agents (Figure 1). These are summarized in a recent single-center study from Hong Kong (4). Diuretics have a clear role to enhance fluid removal but do not protect residual clearance. This patient was maintained on ramipril and bumetanide throughout most of her clinical course. A meta-analysis of existing clinical trials provides evidence that the use of more biocompatible dialysate fluids is associated with better preservation of RRF, although the mechanism is not clear (5). Given that patients who are highly comorbid have a more rapid rate of decline of RRF, this may strengthen the argument to use such fluids, at least for this group. It is important that nephrotoxic agents are avoided where possible in patients who have RRF, although intraperitoneal aminoglycosides to treat peritonitis have inconsistently been linked to reductions in RRF, possibly because severe peritonitis itself is a risk factor.

It has been claimed that PD is better for preservation of RRF than HD, although interestingly, not all studies have shown this finding. The discussion of this topic is complicated by several factors. Among these are the volume status of the comparator HD population; the timing of PD initiation, because for a range of reasons, patients on PD tend to start dialysis earlier than patients on HD; and the effect of late presentation, because such patients are more likely to receive HD (6). Indeed, patients who present late and have not had the opportunity to receive the benefits of predialysis care have higher mortality in the first 1 year after the start of dialysis. From the practical perspective, the presence of a degree of RRF allows for much easier delivery of PD prescription targets in terms of both clearance and volume. Thus, a urine volume of >1 L in 24 hours considerably aids the maintenance of euvolemia. The effective prescription of PD in patients who are anuric is much more challenging and may not be possible for large patients who have slow small-solute transport. When RRF declines, careful attention needs to be given to ensuring adequate volume removal. The European Automated PD Outcome Study of anuric patients provided evidence that UF volumes of <750 ml/d were associated with poorer survival (7). Although targets have been given for 24-hour water removal, it is important that these are individualized, because the object of volume removal is to maintain euvolemia. Fluid restriction is important and considerably aided by dietary salt restriction to <5 g/24 h. However, if it is very strict, it is likely to affect dietary intake and contribute to nutritional deficiency. Indeed, the relationship between sodium removal and outcome is confounded by nutritional status, because patients who clear more sodium have better nutritional parameters and greater RRF (8). Clinicians need to be aware of the potential for RRF to decline, which unless objectively measured, can be overlooked. It is our practice for patients to bring a 24-hour urine collection to each clinic visit; indeed, assessment of the urine volume itself is of practical value.

This patient highlights the importance of RRF to volume management, and she exhibited a number of risk factors for its decline. The period on HD during the last part of 2013 was associated with a stepwise decline in urine volume, renal Kt/V urea, and creatinine clearance (Table 2). Her weight increased during this period from 65 to 70 kg, which was linked to episodes of volume overload. The episode of hypovolemia that she experienced caused by gastroenteritis in July of 2014 had, at least, a reversible effect on RRF. She had a single episode of peritonitis in January of 2014 that was caused by coagulase-negative *Staphylococcus*, and she received two 32-mg intraperitoneal doses of gentamicin as part of treatment.

**Evaluating Peritoneal Membrane Function**

Careful prescription management cannot be delivered without an understanding of small-solute movement across the peritoneal membrane, because it guides decision making regarding the length of the dwell, dialysate glucose concentrations, and the requirement for icodextrin. The most common method of evaluation is the PET, which measures the equilibration of glucose and creatinine over a 4-hour standard 2-L dialysis exchange using either 2.27% or 3.86% glucose dialysate (9). Information obtained from this test includes the evaluation of UF volume, transperitoneal movement of solute, and the rate of catheter flow. Membrane function is classified according creatinine equilibration as fast (≥0.80), average (0.55–0.80), and slow (<0.55) on the basis of 4-hour D/P creatinine ratios (10). Ultrafiltration failure (UFF) is defined from the drain volume that is obtained at the PET as <200 ml from a 2.27% or <400 ml from a 3.86% glucose concentration (11). A potential cause of inaccuracy in volume measurements results from the inclusion by the dialysate manufacturers of approximately 10% extra
volume in dialysis bags, which if not taken into account, leads to an overestimate of UF. Thus, it is important that, during the PET, dialysate bags are weighed before infusion and after drainage to give an accurate measurement of volume. There are numerous variations of the test that aim to give more detailed information, including the deduction of peritoneal capillary aquaporin function. Evaluation of the peritoneal membrane and related prescription management are summarized in a European Best Practice Guideline (10).

Patients who are fast transporters have been shown to have evidence of intraperitoneal inflammation (12) and do less well on continuous ambulatory peritoneal dialysis (CAPD) (13). PD prescriptions for this group use APD to deliver shorter dwell times as well as higher dialysate glucose concentrations to avoid reabsorption of fluid. This is combined with icodextrin for the long dwell. This approach improves outcome in this patient group (14,15). With time on PD, changes to the peritoneal membrane affect the amount of water that moves across the membrane in response to a particular osmotic gradient induced by glucose, which is described as a reduction in the UF capacity. For this reason, sequential evaluation of the PET over time is necessary to inform the most rational prescription, give information regarding UF problems, and provide evidence of long-term peritoneal membrane change.

Icodextrin

One of the most important developments in PD over the last 2 decades has been the introduction of icodextrin as an osmotic agent in PD. Icodextrin is a starch-derived glucose polymer that induces a slower and more sustained UF than glucose (16), with particular benefits for faster transporters. There is high-quality evidence for the benefit of using icodextrin in patients with diabetes who are fast transporters for both technique survival (15) and metabolic control (17). Systematic review confirms improved volume management without a deleterious effect on RRF (18). A randomized, controlled study using icodextrin as part of a glucose-sparing regimen in patients with diabetes showed improved plasma glucose and lipid control, although there was a signal relating to increased volume overload–related adverse events (19). Clearly, although it is important not to overuse dialysate glucose concentrations, it is essential that sufficient UF is achieved to maintain euvoolemia.

Evaluation of Overhydration in PD

Fluid and sodium removal in patients on PD is an important determinant of outcome and seems to have a greater effect than small-solute clearance (3,20). Patients who start dialysis with heart failure have poorer outcomes, and a registry report suggested that this effect may be more marked for patients treated by PD than HD (21). No randomized, controlled trial has addressed this question; however, a possible explanation is that it is easier to both monitor and control volume status in patients on HD because of the closer supervision and UF control that these patients receive.

The clinical evaluation of hydration status is complicated by such factors as vascular stiffness, cardiac dysfunction, hypoalbuminemia, and multimorbidities (Figure 1), creating a need for a more objective measurement of hydration status (22). Bioelectric impedance measures tissue reactance and resistance between electrodes placed on upper and lower limbs and can be used as a tool to monitor hydration status. Resistance between the electrodes is inversely proportional to total body water, whereas reactance is proportional to cell mass. From this, the ratio of extracellular water to total body water is derived, which is used for sequential monitoring, because excess fluid accumulates in the extracellular space. Potential confounding occurs in patients with multimorbidities and inflammation, because muscle wasting leads to a reduction in intracellular water. Poor nutritional status and hypoalbuminemia increase tissue edema, which was a factor in this patient, and it was exacerbated by
the episode of atorvastatin-associated myositis that she experienced. Low serum albumin is an adverse risk factor in patients on dialysis, although for each serum albumin category, the adverse risk is higher for patients on HD than patients on PD (23). Although hydration status measured using bioelectric impedance is a predictor of survival in patients on PD (24), no intervention studies have been reported to date that use it to guide clinical decision-making.

Questions

Dr. James Fotheringham

This patient’s small-solute transport status changed markedly during the course of her PD treatment. What was the pathogenesis of this change and its effect?

M.W.

The four hour D/P creatinine ratio (Table 1) started at 0.95 in February of 2011 before falling to 0.65 in August of that year and rising to 0.74 in April of 2012 and 0.87 in May of 2014. The net UF volumes from those tests were low and met the definition of UFF on each occasion, except for the second occasion, when the D/P creatinine was 0.65 and the net UF volume was 250 ml. A recent longitudinal study of peritoneal membrane function confirmed an early reduction in peritoneal small-solute transfer, followed by a subsequent increase with time on therapy associated with a reduction in transmembrane water movement and a tendency to develop UFF (25). Because small pore number is representative of peritoneal vascular surface area, this suggests an increased vascular surface area, possibly caused by the process of peritoneal neoangiogenesis secondary to dialysate glucose exposure. Support for this comes from a study in which patients who developed a time-dependent increase in D/P creatinine ratio had greater dialysate glucose exposure than those with stable membranes (26). Fluid transport declines, because the increased vascular surface area results in a rapid dissolution of glucose as the osmotic agent. As a consequence, a clinical objective is to develop strategies to reduce dialysate glucose exposure when possible (27).

Dr. Tim Ellam

Is there a target BP that should be aimed for in patients on PD?

M.W.

Evidence in this area is lacking. A study from the United Kingdom Renal Registry of 2770 patients on PD in England and Wales between 1997 and 2004 showed paradoxically that higher systolic and diastolic BPs were associated with reduced mortality in the first 1 year for the whole cohort; however, this effect was reversed in patients who were on the transplant list (28). A protocol of strict salt restriction and UF to control BP resulted in significant improvement in BP control in a group of patients on CAPD but was associated with a reduction in RRF (29). Limited evidence suggests poorer BP control in patients on APD than those on CAPD, presumably because of lower sodium removal on APD; however, this has not been consistently seen. It is difficult, therefore, to give an overall target BP for patients on PD; however, the evidence suggests that BP control should be tighter for patients who are transplant listed.

Dr. Syazrah Salam

What future strategies can be adopted for this patient, and should she continue to be treated with PD? Is there a role for resting the peritoneal membrane? What is the evidence for using a combination of PD and HD in such patients? Would the use of two icodextrin exchanges per day be beneficial?

M.W.

A 3.86% glucose-based dialysate used to be commonly used; however, concern regarding the effect of glucose exposure on the peritoneal membrane (26), patient survival (30), and risk of developing encapsulating peritoneal sclerosis (EPS) (31) has led to a marked reduction in the use of this strength of dialysate, and we do not use it, except for in emergency situations. Clearly, where prognosis is limited, an argument could be made for using 3.86% glucose exchanges, because the relative risk of developing EPS is lower than other risks to which the patient is exposed.

The question of whether peritoneal rest facilitates recovery of the membrane in patients who have developed UFF has been explored in a recent single-center retrospective study (32). The results suggested that it may have a role in early UFF but not after it has become established. De Sousa et al. (32) hypothesized that peritoneal rest may interrupt the process of epidermal-mesenchymal transformation, which is considered to be important in the development of peritoneal membrane change, possibly allowing for its reversal.

The addition of a single weekly session of HD to the PD therapy has been advocated for a range of indications, including fluid overload (33). There is the potential for the UF provided by a weekly HD session to reduce the requirement for hypertonic exchanges, resulting in a longer-term protective effect on the peritoneal membrane. Evidence in this area has been in the form of cohort studies, and it is unlikely that this intervention would ever be subjected to a controlled trial. Our patient tried this approach but did not tolerate the HD sessions well because of cramps.

There is potential that using two exchanges of icodextrin per day would be beneficial, although this is outside the existing licensed indication (34). Concerns include the accumulation of metabolites (maltose and maltotriose) affecting plasma osmolality and lowering plasma sodium. Indeed, given that the licensed daily volume of icodextrin is up to 2.5 L, one could argue that using 2×1.25-L exchanges delivers an equivalent dose.

It is essential that detailed discussion is had with the patient to review her preferences for management given the circumstances of her case. Although we would recommend transfer to HD at this stage, she had difficulty tolerating that modality, and ultimately, her choice to maintain on PD has to be respected. There has been a recommendation to limit time on PD because of the risk of developing EPS; however, the decision should be influenced by patient comorbidity, experience of HD, and suitability of vascular access.

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improves metabolic and fluid management in high and high-average transport diabetic patients. Perit Dial Int 29: 422–432, 2009


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