Understanding and preventing the peritoneal damage caused by conventional dialysis solutions
van Westrhenen, R.

Citation for published version (APA):
van Westrhenen, R. (2005). Understanding and preventing the peritoneal damage caused by conventional dialysis solutions
Chapter 2

**Clinical advantages of new peritoneal dialysis solutions**

Raymond T. Krediet, Roos van Westrhenen, Machteld M. Zweers and Dirk G. Struijk

*Division of Nephrology, Department of Medicine, Academic Medical Centre University of Amsterdam, Amsterdam, The Netherlands*

*Nephrol Dial Transplant 2002; 17 (suppl 3): 16-18*
ABSTRACT

A review is given of the various mechanisms by which conventional glucose/lactate-based peritoneal dialysis solutions can induce damage to the peritoneal membrane. The potential advantages of newly developed dialysis solutions and the results of recent studies on their use in patients are discussed.

KEYWORDS
aminoo acids, bicarbonate, glucose, glucose degradation products, icodextrin, lactate; peritoneal dialysis solutions, pyruvate

INTRODUCTION

A number of studies have reported similar patient survival rates for peritoneal dialysis and haemodialysis when appropriate adjustments are made for differences in case mix [e.g. 1]. However, all studies reported lower technique survival rates for peritoneal dialysis compared with haemodialysis patients [e.g. 2]. Whilst recurrent peritonitis is still the most important reason for transfer from peritoneal dialysis to haemodialysis [3], data from Japan have shown that ultrafiltration failure is the most frequent cause of discontinuation of therapy in long-term peritoneal dialysis patients [4].

The development of ultrafiltration failure with time on peritoneal dialysis is most often associated with increases in the dialysate/plasma (DIP) ratio of low molecular weight solutes such as creatinine [5], suggesting the development of an enlargement of the vascular peritoneal surface area, leading to a rapid absorption of glucose, the standard osmotic agent in dialysis solutions. We confirmed this by the demonstration of a higher number of peritoneal vessels in peritoneal tissue of long-term peritoneal dialysis patients than at the start of treatment [6]. Peritoneal neoangiogenesis could be induced by daily peritoneal exposure to a 3.86% glucose dialysis solution in a 20-week non-peritonitis model in the rat [7]. These observations favour a major pathogenetic role for the currently used peritoneal dialysis solutions.

CONVENTIONAL PERITONEAL DIALYSIS SOLUTIONS

The traditional peritoneal dialysis solutions are bio-incompatible because of their low pH, extremely high glucose and lactate concentrations, hyperosmolality and the presence of glucose degradation products formed during heat sterilization of the solutions. The combination of low pH and lactate appeared to be most toxic in in vitro studies, because it caused a decrease in the intracellular pH [8]. This effect is probably less important in patients, because the instilled solution is diluted immediately with the intraperitoneal residual dialysate volume, leading to a steep rise in pH [9]. Glucose in high concentrations is toxic for the mesothelium both in in vitro and in animal studies [10,11]. Deposition of advanced glycosylation end-products (AGEs) has
been described in peritoneal tissues [12]. Glucose is also likely to be involved in the development of peritoneal neoangiogenesis. This is supported by the diabetiform alterations of the microvessels, that are present in patients [13] and that can be induced in animal models [7]. The finding of local peritoneal production of vascular endothelial growth factor (VEGF) [14], the effluent concentration of which increases with the duration of peritoneal dialysis [15], clearly underlines the similarity with diabetic retinopathy. The clinical importance of this diabetiform peritoneal neoangiogenesis leading to an enlargement of the peritoneal vascular surface area is stressed by the results of Davies et al, who found a relationship between glucose exposure and the development of ultrafiltration failure in their prospective cohort study of continuous peritoneal dialysis (CAPD) patients [16].

Glucose degradation products are toxic to peritoneal cells and induce the formation of AGEs at a faster speed than glucose itself [17]. The relative importance of glucose degradation products to glucose in clinical peritoneal dialysis has not been clarified. Some of the data are summarized in Table 1. Toxicity of lactate has been suggested in in vitro studies comparing pyruvate with lactate. Pyruvate induced less cytotoxicity to peritoneal macrophages and mesothelial cells than lactate [18]. This could be attributed partly to the lower pK_a of pyruvate making it a weaker buffer, but also to its ability to scavenge oxygen radicals [19]. Pyruvate also causes less stimulation of intracellular degradation of glucose in the sorbitol pathway [20]. These data suggest that lactate may contribute to the toxicity of glucose. A possible mechanism is by influencing the intracellular NADH/NAD^+ ratio. NADH is formed from NAD^+ both in glycolysis and in the sorbitol pathway. The resulting increase in the NADH/NAD^+ ratio is reversed by the conversion of pyruvate to lactate, in which NAD^+ is regenerated. NAD^+ is also regenerated in the citric acid cycle. The presence of high lactate concentrations will inhibit the NAD^+ regeneration, leading to an increased intracellular NADH/NAD^+ ratio. An increased NADH/NAD^+ ratio is also present during hypoxia. The latter is a potent stimulus for VEGF [21]. A glucose-induced high NADH/NAD^+ ratio is also called pseudohypoxia [22] and is likely to stimulate the formation of VEGF [23]. This is shown in Figure 1.

**NEW PERITONEAL DIALYSIS SOLUTIONS**

Solutions using amino acids as osmotic agent have been designed to serve as an additional phosphate-free nitrogen source in malnourished patients. They induce only small amounts of ultrafiltration and can only be applied once daily in order to avoid an excessive nitrogen load. The main advantage of including an amino acid-based, lactate-buffered solution in the regular peritoneal dialysis prescription is the reduction in the exposure to glucose and glucose degradation products.
Table 1: An estimation of the relative importance of glucose and glucose degradation products (GDP).

<table>
<thead>
<tr>
<th></th>
<th>Glucose</th>
<th>GDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysate concentration</td>
<td>mmol x 100</td>
<td>μmol x 10</td>
</tr>
<tr>
<td>Mesothelium</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>AGE formation</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Neoangiogenesis</td>
<td>+ + +</td>
<td>?</td>
</tr>
</tbody>
</table>

Figure 1: A schematic representation of the intracellular metabolism of glucose and the resulting effects on the NADH/NAD⁺ ratio.

Icodextrin is a high molecular weight osmotic agent that induces ultrafiltration mainly by colloid osmosis. The 7.5% icodextrin-based, lactate-buffered solution can only be used once daily in order to avoid excessive accumulation of maltose in the circulation [24]. Icodextrin is especially efficient in inducing ultra-filtration during long dwells [24] and in patients with a large peritoneal vascular surface area [25]. This is explained by its low absorption rate from the peritoneal cavity. The use of icodextrin-based solutions is therefore beneficial in patients with ultrafiltration failure caused by a large vascular surface area. Its application also reduces the exposure of the peritoneum to glucose.

The use of dialysis bags with two compartments has made it possible to make solutions that have a higher pH and a reduced concentration of glucose degradation products. Some of them use bicarbonate as a buffer. A glucose/lactate-based solution with a pH between 6 and 7 and a very low concentration of glucose degradation products has been prepared by sterilizing a highly concentrated glucose solution at a very low pH, separately from the other constituents of the dialysis solution. The application of this solution has been investigated in a randomized clinical trial in 80 patients with a maximum follow-up of 2 years. The solution tended to cause less inflow pain and had no effect on parameters of peritoneal transport, but induced alterations in some effluent markers of peritoneal tissues [26]. Cancer antigen 125 (CA 125) increased and dialysate hyaluronan decreased. CA 125 can be considered as a marker of mesothelial cell mass in stable peritoneal dialysis patients [27,28], while hyaluronan may be involved in peritoneal inflammation. These results suggest a better preservation of the mesothelium and less inflammation with the use of this dialysis solution.
Remarkably similar results have been obtained with a glucose-based solution buffered with a combination of bicarbonate and lactate. This solution has a normal pH and contains a reduced amount of glucose degradation products, because the bicarbonate is sterilized separately from the other components of the solution. A randomized clinical trial in 106 patients with a maximum follow-up of 6 months showed less inflow pain, no clinically relevant effects on peritoneal transport and also an increase in dialysate CA 125 and a decrease in hyaluronan [29]. A study in the long-term peritoneal exposure model in the rat revealed less peritoneal fibrosis and neoangiogenesis (unpublished data). The latter may be due to the lower lactate concentration of the solution, leading to less VEGF production. This hypothesis is supported by the results of a pilot study using a glucose-based, pyruvate-buffered dialysis solution in our chronic peritoneal exposure model in the rat (unpublished). The solution resulted in a reduction of the number of peritoneal vessels similar to that of the bicarbonate/lactate-buffered solution. This is shown in Table 2.

Table 2. The mean number of vessels per high power field and the amount of fibrosis, scored semiquantitatively, after 20 weeks of daily i.p. infusion of three different dialysis solutions in Wistar rats

<table>
<thead>
<tr>
<th></th>
<th>3.86% glucose 35 mmol/l lactate</th>
<th>3.86% glucose 25 mmol/l bicarbonate 15 mmol/l lactate</th>
<th>3.86% glucose 40 mmol/l pyruvate</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of vessels</td>
<td>40</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Conclusions**

Long-term exposure to the conventional glucose/lactate-based dialysis solutions can induce damage to the peritoneum. Ultrafiltration failure due to peritoneal neoangiogenesis is the most relevant clinical manifestation of this process. Glucose and glucose degradation products are the most likely causative agents in dialysis fluids. The contribution of other constituents such as lactate is more speculative. The new dialysis solutions are important because their combined use will reduce the exposure of the peritoneum to glucose, glucose degradation products and lactate. The clinical effects of treatment with a combination of these new solutions on the characteristics of the peritoneal membrane are not known yet, but currently are under investigation.


Clinical advantages of new peritoneal dialysis solutions


29. Jones S, Holmes CJ, Krediet RT et al. and the bicarbonate/lactate study group. Continuous dialysis with bicarbonate/lactate based peritoneal dialysis solution is associated with an increase in dialysate CA125 and a decrease in hyaluronic acid levels. *Kidney Int* 2001; 59: 152-1538