Low GDP Solution and Glucose-Sparing Strategies for Peritoneal Dialysis

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Summary: Long-term exposure to a high glucose concentration in conventional peritoneal dialysis (PD) solution has a number of direct and indirect (via glucose degradation products [GDP]) detrimental effects on the peritoneal membrane, as well as systemic metabolism. Glucose- or GDP-sparing strategies often are hypothesized to confer clinical benefits to PD patients. Icodextrin (glucose polymer) solution improves peritoneal ultrafiltration and reduces the risk of fluid overload, but these beneficial effects are probably the result of better fluid removal rather than being glucose sparing. Although frequently used for glucose sparing, the role of amino acid–based solution in this regard has not been tested thoroughly. When glucose-free solutions are used in a combination regimen, published studies showed that glycemic control was improved significantly in diabetic PD patients, and there probably are beneficial effects on peritoneal function. However, the long-term effects of glucose-free solutions, used either alone or as a combination regimen, require further studies. On the other hand, neutral pH–low GDP fluids have been shown convincingly to preserve residual renal function and urine volume. The cost effectiveness of these solutions supports the regular use of neutral pH–low GDP solutions. Nevertheless, further studies are required to determine whether neutral pH–low GDP solutions exert beneficial effects on patient-level outcomes, such as peritonitis, technique survival, and patient survival.

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Glucose is the traditional osmotic agent used in peritoneal dialysis (PD) solutions because it appears safe, has a simple metabolism, and can generate an effective osmotic gradient across the peritoneal membrane. However, in the past 20 years, it increasingly has been recognized that the presence of glucose in PD solutions can lead to a number of undesirable local and systemic effects, as summarized in Table 1.[1]

LOCAL TOXICITY

Long-term exposure to a high glucose concentration in PD solution has a number of direct effects on the structure and function of the peritoneal membrane, which may contribute to the development of peritoneal failure in chronic PD patients. In addition to the direct osmotic stress, a high glucose concentration triggers the formation of amadori products and protein glycosylation, as well as activates the polyol and protein kinase C pathways.[2-4] The end result is mesothelial cell death, local peritoneal inflammation, neoangiogenesis, and progressive fibrosis.[2,5] More importantly, glucose degradation products (GDPs), an inevitable by-product of glucose-containing PD solution during heat sterilization, plays a critical role in protein glycosylation and is probably the key factor that leads to mesothelial cell death and neoangiogenesis.[6,7]

SYSTEMIC TOXICITY

Once absorbed into the systemic circulation, glucose causes a number of metabolic complications including weight gain, hyperglycemia, insulin resistance, dyslipidemia, and appetite suppression.[2,8] Depending on the glucose concentration in the PD solution and peritoneal transport characteristics, approximately 100 to 150 g of glucose, equivalent to 500 to 800 kcal, is absorbed via PD each day.[8] Peritoneal glucose absorption creates a metabolic milieu similar to postprandial hyperglycemia, which may contribute to the development of atherosclerosis and coronary artery disease.[9]

STRATEGIES OF GLUCOSE SPARING: AN OVERVIEW

Given the direct and indirect (via GDP) glucose toxicities, it is prudent to devise strategies for reducing glucose exposure in PD patients.[8] Possible strategies of

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Table 1. Summary of Glucose-Sparing Strategies in PD

Minimization of using hypertonic cycles
Dietary salt and water restriction
Appropriate use of diuretics
Preservation of residual renal function
Glucose-sparing PD solutions
Icodextrin solution
Amino acid–based solution
Combination regimen
Low GDP solutions

glucose sparing are summarized in Table 1. Because glucose is used as an osmotic agent for fluid removal in PD, the use of hypertonic PD cycles could be reduced if the need for ultrafiltration is minimized by dietary salt and water restriction as well as appropriate use of diuretic drugs. Preservation of residual renal function is possible by avoiding the use of nephrotoxic agents (eg, nonsteroidal anti-inflammatory agents and aminoglycosides). Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers also are effective in this regard.[10] On the other hand, peritoneal ultrafiltration could be optimized without excessive exposure to high-concentration glucose solution by appropriate design of the dialysis prescription and, more importantly, the use of glucose-free PD solutions (eg, glucose polymer and amino acid–based solutions). Finally, the use of glucose-containing GDP-free PD solution is another option because much of the glucose toxicity is mediated by GDP.

GLUCOSE POLYMER SOLUTION

Icodextrin is the only commercially available glucose polymer in PD solution. It is a mixture of high-molecular-weight, water-soluble glucose polymers isolated by fractionation of hydrolyzed corn starch.[11] The structure of icodextrin is similar to glycogen, consisting of polysaccharide polymers of D-glucopyranose linked by α-(1→4) and α-(1→6) glucosidic bonds.[12] It is absorbed mainly from the peritoneal cavity via the lymphatic system, and the rate of absorption is much slower than glucose, which is absorbed via the small pores of the peritoneal membrane. Because the osmotic gradient generated by icodextrin dissipates much more slowly than that by glucose, the former often could achieve a much greater net ultrafiltration during the long dwell, especially in patients with high peritoneal transporter status.[13]

A number of clinical benefits have been reported with the use of icodextrin-containing PD solutions,[13] including increased ultrafiltration (especially in high peritoneal transporters),[14,15] improved glycemic control and lipid profiles in diabetic patients,[16,17] improvements in left ventricular geometry,[18,19] enhanced phosphate removal,[20] and probably preservation of peritoneal membrane function.[21] There is also some evidence that using icodextrin solution is associated with better technique survival in PD patients.[22,23] In clinical practice, icodextrin solution is used commonly for the facilitation of fluid removal during long PD dwell, minimization of glucose load in diabetic patients, and preservation of peritoneal membrane function.

Benefits of Ultrafiltration and Fluid Control

The beneficial effect of icodextrin solution on ultrafiltration was reported by Mistry et al [24] in a multicenter randomized control study of 209 patients followed up for 6 months. In this study, the mean ultrafiltration at 12 hours with icodextrin was 5 times greater than 1.35% glucose solution (561 ± 44 versus 101 ± 48 mL; $P < .0001$), and also marginally greater than 3.86% glucose solution (552 ± 44 versus 414 ± 78 mL; $P = .06$), although the latter did not reach statistical significance.[24] Subsequent studies confirmed that the beneficial effect on ultrafiltration was sustained.[22,25] For example, in a multicenter randomized control trial on 59 patients followed up for 1 year, Paniagua et al[25] reported that ultrafiltration was higher in patients using icodextrin solutions for the long dwell than in patients using glucose solutions throughout 1 year despite more frequent use of solutions with a glucose concentration higher than 1.5% in the latter group. With slightly different inclusion and exclusion criteria, two meta-analyses also showed the superiority of icodextrin in maximizing ultrafiltration during the long dwells of both continuous ambulatory PD and automated peritoneal dialysis patients compared with dextrose-based solutions.[14,15]

The expected consequences of better ultrafiltration are less fluid accumulation and better blood pressure control, which have been supported by several small studies. For example, Woodrow et al[26] showed that use of icodextrin for the daytime dwell in automated peritoneal dialysis resulted in improved fluid balance, with better estimates of total body water, extracellular water (ECW), and the extracellular/intracellular water ratio by bioimpedance spectroscopy study, as compared with 2.27% glucose analysis. Similarly, Paniagua et al[25] observed a faster and deeper reduction in total body water in patients treated with icodextrin solutions than in patients treated with glucose solution. After 1 year of follow-up evaluation, icodextrin-treated patients had a significant and stable reduction in ECW as compared with baseline, whereas ECW remained unchanged in the glucose group.[25] Reductions in ambulatory blood pressure and left ventricular end-diastolic diameter also were found in the icodextrin group of this study.[25] In another recent randomized