Chapter 5
The Evolution of Peritoneal Dialysis Solutions

Ephantus Njue, Lewis Simon, and Mohammad Kamgar

The use of peritoneal dialysis (PD) solutions was first described by Wegner, a German investigator in the late nineteenth century. He injected hypertonic and hypotonic solutions into the peritoneal cavity of a guinea pig and observed that hypertonic solutions increased the volume in the cavity and hypotonic solutions decreased the volume. Wegner's findings triggered interest in the use of solutions for the treatment of uremia. Several scientists followed suit; Ganter used saline to treat uremia, and Heusser added dextrose to increase ultrafiltration (UF). Rhoads added lactate in PD solutions as a buffer to correct acidosis in 1938. The use of PD solutions has continued to evolve to the present day in the quest for formulating an optimal dialysate. The durability of PD as a dialysis modality depends on the type of solution utilized and its long-term effects on the peritoneal membrane. Many have argued that biocompatible solutions are ideal because they are proposed to limit the long-term degradation of the peritoneal membrane.

PD solutions are used as osmotic agents to regulate UF by increasing or decreasing the tonicity as needed. The fluid is used to treat uremia through diffusion and convective transport across the membrane. The commercially used solution in the United States is the traditional dextrose-based solution composed of water, osmotic agents (glucose), electrolytes, and minerals. In addition, they have low PH for the purposes of preservation and prolonging shelf life. There has been a slow uptake for neutral or biocompatible solutions worldwide; the reasons for this will be explored later in this chapter. Ideal PD solutions would promote and position PD on an equal footing with other kidney replacement modalities in terms of longevity.

E. Njue (✉)
UCLA CORE Kidney Health Program, Los Angeles, CA, USA
e-mail: enjue@mednet.ucla.edu

L. Simon · M. Kamgar
CORE Kidney Health Program, Department of Medicine, Division of Nephrology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

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According to Vanholder [6], an ideal PD solution must possess the following characteristics:

- Have a sustained and predictable solute clearance with minimal absorption of the osmotic agents.
- Supply deficient electrolytes and nutrients if required.
- Correct acid-base problems without interacting with other solutes in the PD fluid.
- Be free of and inhibit the growth of pyrogens and microorganisms.
- Be free of toxic metals.
- Be inert to the peritoneum.

Unfortunately, the most commonly utilized PD solutions are far from ideal. They are highly acidic, are glucose-based, are easily absorbed, contain glucose degradation products (GDPs), wash out local antibodies, and are difficult to add buffers due to crystallization. The solutions also contain dextrose in varying concentrations, which generates GDPs during the sterilization process. The systemic effects of GDPs include myocardial toxicity; locally, they cause mesothelial cell proliferation, increased production of advanced glycation end products (AGES), and vascular endothelial growth factor (VEGF). Topley [5] opined that the structural or "fibrotic" changes within the peritoneal membrane result in the alteration of its transport characteristics. The aggregate effects of these by-products include inflammation, fibrosis, vascular proliferation, and ultimately UF failure.

Composition of PD Solutions

Osmotic Agents

Ultrafiltration (UF) is a critical component of dialysis in order to avoid extracellular fluid volume overload. By creating an osmotic gradient, UF is achieved by a glucose concentration gradient in PD solutions versus the plasma glucose levels. The degree of UF is dependent on the concentration gradient wherein higher glucose concentration creates a higher gradient leading to flux of water from the vascular compartment into the peritoneal cavity. This gradient for UF dissipates as glucose is absorbed in the opposite direction along its own concentration gradient. Blood glucose control is a critical factor for UF; hyperglycemia can lead to increased fluid absorption leading to fluid overload. Osmotic gradient can be increased by using solutions with higher osmolarity. Glucose, therefore, is not an ideal osmotic agent because it is rapidly absorbed, worsens metabolic effects, and is difficult to utilize in labile diabetic patients. An ideal osmotic agent should be metabolized easily with nontoxic degradation products, poorly absorbed, inert and non-toxic to the peritoneal membrane, and inexpensive. In addition, such a product must be effective at low concentrations with no metabolic consequences of absorption and must be of nutritional value if absorbed. Several osmotic agents have been used throughout the history of PD including glucose, saline, amino acids, mannitol, polyglucose, and sorbitol.

Glucose is the most commonly used osmotic agent in PD and is available in North America in three different dextrose concentrations: 1.5, 2.5, and 4.25 percent. It is not an ideal osmotic agent due to it being easily absorbed (hence rapidly dissipating the osmotic gradient for UF) and the associated metabolic complications from its absorption including hyperglycemia, hyperlipidemia, and weight gain. These high glucose concentration solutions, low pH, and GDP production can affect peritoneal host defense mechanisms by inhibiting phagocytosis and bactericidal activities. These "unphysiologic" characteristics of PD fluids have been associated with significant loss of peritoneal mesothelial cell viability and function, compromised peritoneal immune system components, and promotion of fibrosis [1].

The advantages of traditional dextrose-based PD solutions are primarily associated with its cost-effectiveness, safety, and availability. The long-term effects of these solutions on the peritoneal membranes are consequential; some studies have associated them with terminal membrane failure including encapsulating peritoneal sclerosis. The use of conventional PD fluids, characterized by acidic pH (5.0–5.8), high lactate concentrations (30–40 mmol/L), high osmolality (320–520 mOsm/kg), high glucose concentrations (75.5 to 214 mmol/L), and contamination by GDPs, may contribute to these adverse outcomes [1]. However, cost and availability have remained impediments for use of biocompatible PD solutions.

Fluid removal with PD is mainly achieved via convection, and water removal from plasma exceeds sodium removal in the first few hours of a dwell, often leading to hypernatremia. Therefore, the relatively low sodium level in PD solutions helps offset the tendency for hypernatremia. Relatively low calcium concentrations can aid in the treatment of hyperphosphatemia by allowing the patient to use calcium-containing phosphorus binders without the risk of systemic hypercalcemia. However, hypocalcemia may develop in some patients, particularly in those with poor compliance in taking calcium-containing phosphorus binders as prescribed. The use of a lower concentration of magnesium is designed to prevent hypermagnesemia and bone disease. Lactate is commonly used to control acidosis by supplying an absorbed buffer that is quickly converted to bicarbonate in the liver.

The constituents of these solutions are listed in Table 5.1.

Two common commercially available solutions in North America are Dianeal by Baxter and Delflex by Fresenius. For CAPD, they are available in 1-liter, 2-liter, 2.5-liter, and 3-liter sizes, and for APD, they are available in 3-liter, 5-liter, and 6-liter sizes.

Table 5.1 Constituents of PD solutions

Dextrose (%)	1.5, 2.5, 4.25
Sodium (mEq/L)	132
Chloride (mEq/L)	2.6
Magnesium (mEq/L)	0.5, 1.5
Lactate (mEq/L)	35, 40
Calcium mEq/L	2.5, 3.5
pH	5.2, 5.6

Adapted from Guest [3]

Neutral pH solutions (biocompatible solutions) are not commonly used in North America, and many are not even available for use. They produce lower levels of GDPs, and it is postulated that they effect minimal mesothelial cell damage. This may suggest that patients could stay longer on PD with these solutions, but this is unproven. Indeed, in studies of technique failure in PD, problems with the integrity of the peritoneal membrane rank very low on the list of causes. Theoretically, biocompatible solutions should have better outcomes than traditional glucose-based solutions. In addition to utilizing lactate as a buffer, sodium bicarbonate is added in a separate chamber within the solution bag to prevent calcium and magnesium carbonate precipitation. The chamber is broken just before starting dialysis. Examples of these products are Physioneal, Balance, bicaVera, and Gambrosol Trio.

The amino acid-based solutions contain the same electrolytes as glucose-based solutions and have the same lactate buffer. They come in 0.5 to 2 percent concentrations. Since they are colloids, they have relatively strong osmotic properties compared to crystalloids. They are designed for patients at high risk for protein loss, such as high transporters, and also help with blood glucose control and reduce overall insulin demand. The primary disadvantage of amino acid-based solutions is uremia due to increased amino acid absorption, which can potentially lead to metabolic acidosis. These products are most often used as a nutritional supplement and are utilized in addition to a standard glucose-based PD solution. There is controversy surrounding the use of amino acid-based solutions and whether they contribute in any way to nutritional status, and because of this, most practices do not utilize these products. The current commercially available amino acid-based solution is Nutrineal through Baxter.

The polyglucose solutions are made up of glucose polymers, and due to their molecular size, they are not able to cross the peritoneal membrane. These solutions act as colloids and have an osmolarity of 285–286 mOsm/L. For this reason, polyglucose solutions are able to sustain an oncotic gradient leading to sustained UF. These solutions require a long dwell time because of the sustained oncotic gradient. Thus, the pressure created by these solutions will decline only slowly during the dwell, and a positive net UF is therefore sustained throughout the long dwell [2]. The current commercially available polyglucose solution is Extraneal (icodextrin) supplied by Baxter. It is traditionally used as a last fill or a single manual exchange for a long dwell. Despite its impressive UF characteristics, it has somewhat restricted use due to cost. Recently, as more physicians have become aware of its unique characteristics and potential benefits to PD patients, there has been an increase in utilization. In most organizations, it requires a non-formulary exception request to be approved before it can successfully be prescribed. Icodextrin is slowly absorbed though the lymphatic system and degraded by serum amylase into glucose. In the event of suspected pancreatitis in this patient population, evaluation of serum lipase instead of serum amylase is recommended. This is because serum amylase may not increase in patients on icodextrin, thus making the evaluation of serum amylase levels an ineffective means of diagnosing pancreatitis in these patients. Icodextrin has a black label from the US Food and Drug Administration (FDA) due to its potential for producing false glucose readings with GDHPQQ

glucose monitors. It is critical that patients on icodextrin ask their endocrinologist for an appropriate glucose monitor to avoid these false readings. While in the hospital, blood sugar should be checked using peripheral blood draws unless the ward glucometers are compatible with icodextrin. After the discontinuation of icodextrin, its effects on serum glucose can persist for up to 2 weeks. Patients using icodextrin need to always have a safety warning device with them that can alert providers about the potential artifactual elevation of serum glucose secondary to icodextrin metabolites in systemic circulation.

Conclusion

Peritoneal dialysis (PD) is a widely accepted dialysis modality with superior health outcomes compared to hemodialysis in the short term. The sterilization process of glucose-based solutions leads to increased production of GDPs and AGES, potentially leading to peritoneal membrane damage. The earliest symptom of PD failure is a reduction in UF. The use of biocompatible solutions, theoretically, should increase the duration of integrity of the peritoneal membrane and make PD a feasible choice as a long-term dialysis modality. William et al. [7] demonstrated that a new PD solution delivered to the peritoneum at neutral pH, and containing significantly lower levels of GDP, may significantly improve the homeostasis of the peritoneal cavity. However, recent clinical trials by Schaefer et al. [4] report a different story from the remarkable peritoneal biopsy study carried out in multiple pediatric nephrology centers across Europe. The study concluded that neutral-pH, low-GDP PD fluids induce early inflammation, epithelial-to-mesenchymal transition (EMT), and marked vascularization of the peritoneum, all of which are associated with peritoneal membrane transport function. Although the study was carried out in a pediatric population and the same factors might not necessarily apply to the adult population, its findings still create doubts regarding the negative effects that biocompatible solutions may have on peritoneal membrane's long-term integrity and function. Further clinical trials on biocompatible solutions will ultimately determine the future use of these products.

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