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Biocompatible Solutions for Peritoneal Dialysis

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1. Introduction

In 1978, a simplified technique for peritoneal dialysis (PD) using plastic bags and glucose as osmotic agent allowed PD to become accepted as a home-based renal replacement therapy. However, PD was marred by complications including peritonitis and loss of function of the peritoneal membrane. Both complications may be favored by the bioincompatibility of PD solutions. The composition of PD solutions has evolved over the years, building on a better understanding of the biocompatibility and of technical advances that enable the commercial viability of certain solutions. The main osmotic agent used to obtain ultrafiltration is glucose. Conventional glucose-containing PD solutions are lactate-buffered, acidic pH solutions presented in single chambered bags. The use of new manufacturing techniques, buffer presentation, and new osmotic alternatives to glucose have resulted in more biocompatible glucose containing PD solutions that have a lower concentration of glucose degradation products (GDP) and a neutral, more physiological pH, as well as in glucose-free solutions.

2. Composition of PD solutions

PD solutions are sterile and contain water, electrolytes, a buffer and an osmotic agent (Table 1). Electrolyte concentrations (Na^+, Cl^-, Ca^{++}, Mg^{++}) display little variation between different PD solutions.

- Water
- Electrolytes: Na^+, Cl^-, Ca^{++}, Mg^{++}
- Buffer: lactate, lactate / bicarbonate or bicarbonate
- Osmotic agent glucose, icodextrin or amino acids
- Glucose degradation products (GDPs) are not added on purpose, but are generated during heat sterilization, especially in conventional glucose-containing solutions.

Table 1. Composition of PD Solutions

PD solutions contain an osmotic agent that allows a negative balance of fluids (ultrafiltration). Glucose is the most widely used osmotic agent. The only alternative osmotic agents available are 7.5% icodextrin and a 1.1% amino acid mixture (Frampton, J. E. et al.

2003) (Tjiong, H. L. et al. 2005). Neither avoids the use of glucose as only one daily exchange of each glucose-free PD solution can be used. There are solutions with three different concentrations of glucose in order to individualize ultrafiltration. The highest concentrations of glucose obtains more ultrafiltration, but also enhances the adverse effects of glucose and in conventional solutions, of the GDPs. The glucose concentration of each of the three types of solutions varies with the manufacturer and ranges between 1360 and 4250 mg / dl, resulting in an osmolarity of 345 to 511 mOsm / L. There is some confusion in the literature regarding the concentration of glucose in the various solutions because in America it is expressed as the concentration of dextrose (glucose monohydrate with a molecular weight of 198 Da), and in Europe as the concentration of glucose (anhydrous glucose molecular weight 180 Da). Thus a dextrose concentration of 1.5%, 2.5% and 4.25% is the same as a glucose concentration of 1.36%, 2.27% and 3.86% respectively, but a concentration of glucose 1.5% corresponds to 1.65% dextrose.

Lactate is the most common buffer in PD solutions. Recently solutions buffered with lactate / bicarbonate or bicarbonate alone have been marketed, presented in bicameral bags to keep separate the bicarbonate from calcium and magnesium until just before the infusion, thereby avoiding precipitation (Fig. 1) (Montenegro, J. et al. 2006; Feriani, M. et al. 1998; Montenegro, J. et al. 2007; Tranaeus, A.2000; Schmitt, C. P. et al. 2002; Pecoits-Filho, R. et al. 2003; Otte, K. et al. 2003). Bi- or tricameral bags also allow the separation of glucose and buffer until just before the infusion. Thus, glucose is contained in a low pH chamber and the buffer in a high pH chamber. The use of acetate as a buffer was abandoned years ago due to undesirable effects including vasodilation, decreased myocardial contractility, and sclerosing peritonitis.
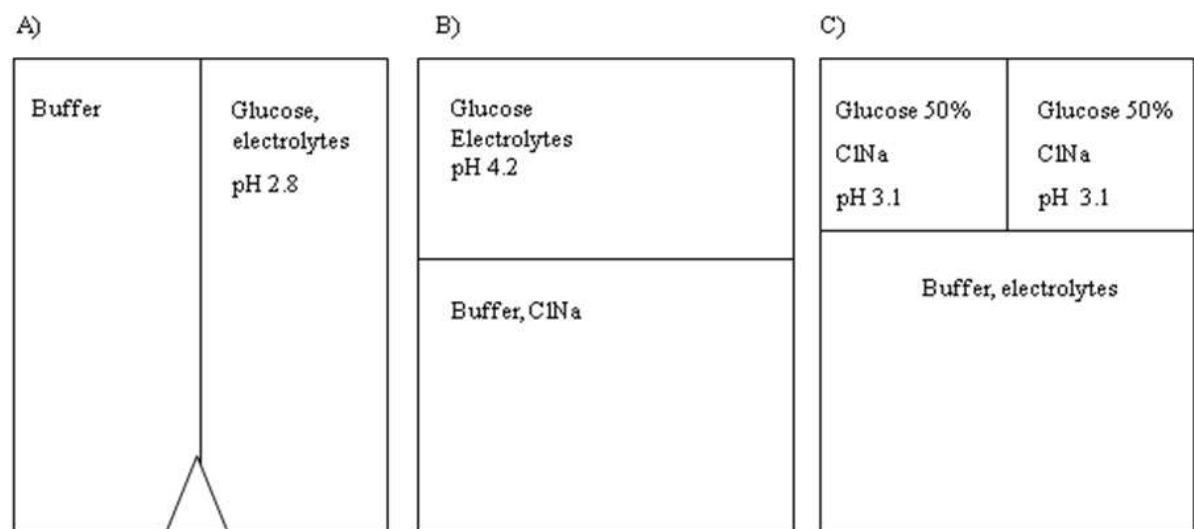

Fig. 1. **Bicameral and tricameral PD bags. A and B**) Bicameral bags. **C)** Tricameral bags. Bi- and tricameral bags are used to manufacture biocompatible PD solutions. Separating glucose form the buffer allows heat sterilization of the bags while minimizing the generation of GDPs.

3. Biocompatibility

Biocompatibility is the ability of a technique or system to fulfill its function without causing a clinically significant adverse response of the host. In PD the concept was initially applied

to the influence of PD solutions on the biological responses of peritoneal tissues and cells, and the morphology and function of the peritoneum (Holmes, C. J. et al. 2003). In addition PD solutions may also have systemic adverse effects (Pecoits-Filho, R. et al. 2003). Conventional solutions are bioincompatible mainly due to the high concentration of glucose and GDPs. The low pH, high osmolarity and the presence of high concentrations of lactate also contribute to bioincompatibility (Table 2). These factors may cause adverse effects on celular systems, including dysfunction and death of mesothelial cells and leukocytes. In this regard, GDPs are the most lethal factor (Ortiz, A. et al. 2006).

The consequences of bioincompatibility include worsening of peritoneal defense against infection and injury, loss of peritoneal mesothelial cells, epithelial-mesenchymal transformation (EMT) of mesothelial cells, fibrosis, diabetiform changes of vessels and possibly peritoneal sclerosis (Yanez-Mo, M. et al. 2003; Catalan, M. P. et al. 2001; Williams, J. D. et al. 2002). Among systemic consequences we find increased circulating advanced glycation products (AGEs), glucose metabolic effects, and poorer preservation of residual renal function (Montenegro, J. et al. 2007; Williams, J. D. et al. 2004; Kim, S. G. et al. 2008; Zeier, M. et al. 2003).

> High concentration of glucose
> Glucose degradation products (GDPs)
> High osmolarity
> Acid pH
> Lactate

Table 2. Elements contributing to the poor biocompatibility of PD solutions

New solutions have been designed with a neutral pH, without lactate, lack of glucose and/or low concentrations of GDPs (Table 3)(McIntyre, C. W.2007; Montenegro, J. et al. 1993).

	Conventional	New Solutions Alternative osmotic agents	New Solutions Biocompatible dextrose
Container	Unicameral	unicameral	bi or tri-cameral
Osmotic agent	Glucose	Icodextrin, amino acids	glucose
GDPs content	High	low or no	low
pH	5.5	5.8 to 6.5	6.3 to 7.4
Buffer	lactate	lactate	lactate, bicarbonate, lactate/bicarbonate

Table 3. PD Solutions

Biocompatibility of new solutions has been amply demonstrated in studies in cultured cells and animal models and they are expected to improve peritoneal defense and survival of the peritoneal membrane function and residual renal function. Clinical experience so far in clinical trials, though still incomplete, tends to support these expectations (Table 4).

PD solutions plastic bags may also contribute to bioincompatibility, although the precise contribution has not been established. The conventional material the bags are made of is PVC (polyvinyl chloride). PVC is difficult to recycle and contains plasticizers such as phthalic acid. Phthalic acid released from the bags can eventually be absorbed from the peritoneum (Mettang, T. et al. 2000), although it is unclear whether this represents a health risk. New

materials, such as Biofine ®, a polyolefin which needs no plasticizers, Steriflex ® or Clearflex ® are thought to be more biocompatible. Conventional bags are single chambered and filled with the dialysis solution composition that is infused into the peritoneum (NO CITATION DEFINITION). The new glucose solutions are packaged in bi or tricameral bags and the contents of the chambers is mixed just before infusion into the peritoneum (Fig 1). This allows to sterilize glucose at low pH, thus decreasing the production of GDPs, and to separate the calcium and magnesium from bicarbonate to avoid precipitation.

Surrogate markers	
	Increased CA125 biomarker in the peritoneal effluent (Williams, J. D. et al. 2004; Fusshoeller, A. et al. 2004; Jones, S. et al. 2001; Haas, S. et al. 2003; Rippe, B. et al. 2001)
	Lower circulating AGEs (Fusshoeller, A. et al. 2004; Williams, J. D. et al. 2004)
	Better correction of acidosis (Montenegro, J. et al. 2006; Tranaeus, A.2000; Otte, K. et al. 2003; Carrasco, A. M. et al. 2001; Haas, S. et al. 2003)
	Better preserved residual renal function (Montenegro, J. et al. 2007; Williams, J. D. et al. 2004; Kim, S. G. et al. 2008)
	No change (Fan, S. L. et al. 2008)
Clinical Results	
	Mortality decreased (Lee, H. Y. et al. 2005; Lee, H. Y. et al. 2006)
	Decreases peritonitis rate (Montenegro, J. et al. 2007; Ahmad, S. et al. 2006)
	No change (Lee, H. Y. et al. 2006; Lee, H. Y. et al. 2005; Fan, S. L. et al. 2008; Rippe, B. et al. 2001)

[1] No clinical trials have been published whose primary objective is the study of these items

Table 4. Beneficial effects of new glucose solutions in clinical practice

3.1 GDPs

GDPs are the main contributors to the bioincompatibility of PD solutions. Heat sterilization of the solutions facilitates the formation of GDPs, especially if the pH of the glucose chamber is high. GDPs are small molecules generated from glucose (Table 5 and Fig. 2). Many GDPs are toxic and more reactive than glucose with proteins to form AGEs such as pentosidine, N (epsilon) - (carboxymethyl) lysine (CML) and others. AGEs cause protein dysfunction and activate a specific receptor (RAGE, receptor for AGE) which transmits intracellular signals that modify cell behavior. Several GDPs are toxic, but only 3,4-dideoxyglucoson-3-ene (3,4-DGE) has been shown to be lethal for leukocytes and mesothelial cells at the concentrations usually found in commercial PD bags (Justo, P. et al. 2005; Santamaria, B. et al. 2008; Catalan, M. P. et al. 2005). 3-deoxyglucosone (3-DG), the precursor of the 3,4-DGE, is also cytotoxic, although high concentrations (around 500 µM) are needed to observe cytotoxicity. These high concentrations have not been found by most authors in the PD solutions tested (Table 5).

The concentration of GDPs depends mainly on the pH of sterilization of glucose, on glucose concentration (higher GDP generation in solutions containing 4.25% glucose than in 1.5% glucose solutions) and on storage temperature (Erixon, M. et al. 2006; Erixon, M. et al. 2005; Erixon, M. et al. 2004). The lower the pH of sterilization of glucose, the lower the generation of GDPs. The optimal pH of sterilization to decrease the production of GDPs is

GDP	Conventional glucose[1]	Biocompatible glucose[1,2]	Icodextrin	Aminoacids
3-deoxiglucosone	172-425	10	4-11	<0.2
3,4-DGE[3]	10-125	0.2-0.5	3	<0.2
5-HMF	6-15	10 to 19	2	-
Methylglyoxal	2-12	<1	1.5	<0.2
Glyoxal	<3-14	<1	2.5	<0.2
Acetaldehyde	120-420	<2	37	-
Formaldehyde	7-13	<3	9	-

[1] The range represents the values for glucose solutions with concentrations around 1.5 to 4% and measurements made by different authors.
[2] Excludes Physioneal that has higher values.
[3] The wide range observed depends on the concentration of glucose as the time since the sterilization and storage conditions
Ref: (Erixon, M. et al. 2006)

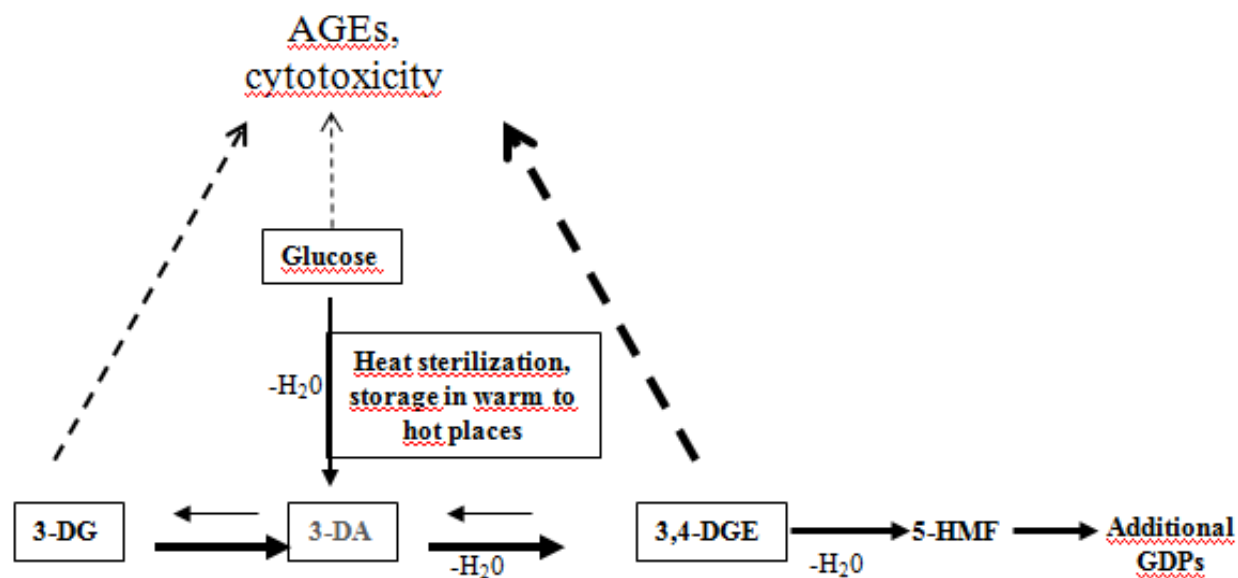Table 5. GDP content in μmol / L of different solutions PD

Fig. 2. **GDP generation from glucose in PD fluids during heat sterilization and storage**. Successive dehydration steps of the glucose molecule lead to initial GDPs and these are subsequently degraded into smaller molecules. There is a temperature-dependent balance between 3-DG, 3-DA and 3,4-DGE. Increasing temperature shifts the equilibrium to the right, towards the most toxic compound, 3,4-DGE. High concentrations of glucose are cytotoxic and lead to AGE formation, but 3-DG and, above all, 3,4-DGE lead to higher cytotoxicity and AGE generation. The thick dashed lines represent the ability to induce biological effects. 3-DG: 3-deoxyglucosone, 3-DA: 3-deoxyaldos-2-ene, 3,4-DGE: 3,4-dideoxyglucosone-3-ene, AGE: advanced glycation products. HMF: hydroxymethylfurfural. Adapted from reference (Ortiz, A. et al. 2006). Additional GDPs include furaldehyde, formaldehyde, acetaldehyde, methylglyoxal, glyoxal.

2.0 to 3.1 (Erixon, M. et al. 2006). It is not possible to achieve a pH so low in unicameral bags, since solutions at such low pH cannot be safely infused into the peritoneum. Therefore, conventional glucose-containing unicameral bags have a pH of approximately 5.5 and a high concentration of GDPs. The problem was solved using bi-or tricameral bags, which allow sterilization of the glucose solution in a low pH chamber, separated from the buffer which is contained in a compartment at high pH (Fig. 1). This system allows both to lower the production of GDPs and, by mixing the contents of both chambers before the infusion, to infuse a solution at more physiological pH (6.3 to 7.4).

The concentration of the most toxic GDP identified so far, 3,4-DGE, varies with storage temperature conditions: it is higher immediately post-heat sterilization, reaches a nadir at 2 months of storage at room temperature (25 ° C), but may rise again if the bag is exposed for hours at higher temperatures (Erixon, M. et al. 2005). These higher temperatures may be reached during the summer at patient's homes or during transportation. This has rekindled interest in transport and storage temperature of the solutions, especially in the summer months. This problem with sterilization and storage temperatures is not observed with the newer bicameral or tricameral having a pH <3.0 in the glucose chamber.

4. Conventional PD solutions

Conventional solutions are those contained in unicameral bags, with glucose as an osmotic agent and lactate as buffer. These solutions have a low pH and high GDP content and present the biocompatibility problems mentioned in previous sections, in addition to the continuous glucose absorption from the peritoneum and the high concentration of intraperitoneal glucose.

4.1 Glucose as osmotic agent

Glucose is the only osmotic agent which has proved safe and effective for chronic use in multiple exchanges within a 24 hour period. It is cheap and provides calories. However, it is not the ideal osmotic agent and poses several problems. Thus, the high concentrations of glucose required to induce ultrafiltration may facilitate or exacerbate:

- Hyperglycemia with hyperinsulinemia, as well as undetected peaks of hyperglycemia in diabetics
- Hyperlipidemia
- Obesity
- Conventional solutions damage the long-term peritoneal membrane, although in most studies it is not possible to tell apart the effect of glucose from the effect of GDPs (Davies, S. J. et al. 2001).

In addition, glucose-containing PD solutions are not effective in promoting ultrafiltration in patients with high peritoneal transport. This is so because the high transporters absorb glucose from the peritoneum at a faster rate, thus dissipating the osmotic gradient that favours ultrafiltration earlier. Glucose uptake varies with the type of peritoneal transport of small solutes, which is a patient-specific feature (high transporters absorb more), with the dwell time (higher amounts of glucose are absorbed in more prolonged exchanges) and the concentration of glucose in the bag. It has been estimated that the average patient on CAPD absorbs from the peritoneum between 100-200 g glucose/24 h (about 8 kcal / kg / d) (Dombros, N. et al. 2005).

4.2 pH

Conventional dextrose solutions have a pH of 5.5 (range 5-6). The low pH prevents caramelization of glucose during heat sterilization and reduces, but does not prevent the generation of GDPs. A lower pH may decrease GDP generation, but causes pain during infusion and possibly other adverse effects in the longer term. In fact, the pH of 5.5 causes pain in some patients. This pH is rapidly buffered by bicarbonate which diffuses from the circulation into the peritoneal cavity, reaching on average 7.0 in 30 minutes and above 7.30 in 90-120 minutes (Schmitt, C. P. et al. 2002). The new PD solutions with higher pH are painless during infusion and the pH is already physiological during infusion or is normalized faster.

5. New PD solutions

We distinguish two approaches to the design of new PD solutions (Table 3) (McIntyre, C. W.2007; Montenegro, J. et al. 1993). One is to use of bi- or tricameral bags to improve glucose solutions, so that GDP content decreases and final pH approaches physiological values, with or without a total or partial change of the buffer. The other is to replace glucose by other osmotic agents such as icodextrin or amino acids, keeping lactate as buffer.

The aim of this greater biocompatibility is to achieve better clinical results. The advantages of the newer, more biocompatible have been well documented in cell culture and animal studies. However, the big differences observed in basic research are more difficult to convincingly demonstrate in humans and some studies have failed to show such superiority.

5.1 Biocompatible glucose solutions presented in bi- or tricameral bags

Bi or tricameral bags allow to sterilize glucose at low pH and separate the bicarbonate (when present) from calcium and magnesium (Fig. 1). The differential characteristics of biocompatible glucose-containing solutions contained in bi or tricameral bags versus conventional, bioincompatible solutions are basically three: the low GDP concentration, a more physiological final pH, often around 7-7.4; and, in some cases, a pure bicarbonate or bicarbonate plus lactate buffer.

However, not all biocompatible glucose solutions presented in bi- or tricameral bags areequal and their impact on clinical parameters should be assessed individually. Thus, there are differences in glucose concentration, buffer (bicarbonate, bicarbonate/lactate or lactate), pH of the glucose chamber and, thus, in GDP content, and in the final pH of infusion of the solutions, once the contents of all the chambers has been mixed pre-infusion is more physiological (6.3-7.4).

Advantages and indications. The main advantage of these solutions is greater biocompatibility resulting from the low concentration of GDPs, physiological pH and, in some cases, absence of lactate. More biocompatibility suggests that these solutions should be the choice if there are resources to pay for them. Their use has resulted in improvement in surrogate parameters in clinical trials and observational studies including a higher peritoneal effluent concentration of CA125 (considered by many as a marker of mesothelial mass), lower rate of apoptosis in the effluent, lower concentration of circulating AGEs, better control of metabolic acidosis, better preservation of residual renal function, lower incidence of peritonitis, and in Registry studies, lower mortality (Table 4) (Montenegro, J. et al. 2007; Montenegro, J. et al. 2006; Williams, J. D. et al. 2004; Kim, S. G. et al. 2008; Lee, H. Y.

et al. 2005; Navarro, J. F. et al. 1999; Rippe, B. et al. 2001; Fan, S. L. et al. 2008; Ahmad, S. et al. 2006; Carrasco, A. M. et al. 2001; Fusshoeller, A. et al. 2004; Jones, S. et al. 2001; Haas, S. et al. 2003). As indicated above, the different characteristics of the various commercially available biocompatible solutions do not allow concluding that the observed effects are class effects. However, there are no direct clinical comparisons between the different solutions (from different providers) on the market and currently available information is incomplete, since not all possible effects have been studied with all the solutions. The effect on residual renal function has been the focus of three long-term randomized studies (12-18 months) with three solutions of different characteristics (Kim, S. G. et al. 2008; Fan, S. L. et al. 2008). Solutions with lower content GDPs better preserved residual renal function (Kim, S. G. et al. 2008).

Several experimental reports support the bioincompatibility of conventional PD solutions (heat-sterilized glucose-containing solutions). Prolonged exposure to conventional PD solutions exert deleterious effects on the peritoneum, including loss of mesothelial cell monolayer, submesothelial fibrosis, angiogenesis, hyalinizing vasculopathy and impaired viability and function of human peritoneal mesothelial cells (HPMC) and leukocytes (Jorres A KI 2008 (Yanez-Mo, M. et al. 2003; Vargha, R. et al. 2006; Santamaria, B. et al. 2008; Williams, J. D. et al. 2002). The adverse effects may lead, in the long-term to ultrafiltration failure and PD technique withdrawal. GDPs have been identified as the major cytotoxic agents in conventional PD solutions. GDPs impair viability, cell function, cytokine release on HPMC, induce apoptosis and promote EMT in mesothelial cells and impair leukocyte function and viability (Amore, A. et al. 2003; Witowski, J. et al. 2000; Witowski, J. et al. 2001; Witowski, J. et al. 2001; Morgan, L. W. et al. 2003) (Oh, E. J. et al. 2010). In addition, the number of mesothelial cell dying by apoptosis is increased in the effluent of patients using high GDP PD solutions vs. patients using low GDP PD solutions (Santamaria, B. et al. 2008). 3,4 deoxyglucosone-3 ene (3,4 DGE) is the main cytotoxic product in conventional PD solutions. 3,4 DGE accelerates leukocyte and HPMC apoptosis, to the same extent as conventional PD solution, retards remesothelization and may compromise peritoneal defense (Santamaria, B. et al. 2008; Catalan, M. P. et al. 2005; Morgan, L. W. et al. 2003; Linden, T. et al. 2002; Yamamoto, T. et al. 2009). The poor biocompatibility of PD solutions may also compromise peritoneal defenses and promote peritonitis or a poor resolution of peritonitis episodes. At the molecular at cellular level peritonitis is characterized by cytokine release and leukocyte recruitment to the peritoneal cavity (Zemel, D. et al. 1996; Li, F. K. et al. 1998). However neutrophils die spontaneously by apoptosis at sites of inflammation and accelerated leukocyte apoptosis may impair the peritoneal defense. Indeed bioincompatible PD solutions accelerate neutrophil apoptosis and this has been shown retard recovery from *S aureus* peritonitis in mice exposed to PD solutions (Catalan, M. P. et al. 2003). Neutrophil apoptosis is a physiologic process that limits inflammation. However, premature neutrophil apoptosis may compromise the antibacterial potential of these leukocytes. Conventional PD solutions accelerated leukocyte apoptosis in vivo and in vitro (Catalan, M. P. et al. 2003; Catalan, M. P. et al. 2005). In vitro studies, also show that 3,4 DGE accelerated neutrophils and mononuclear cell apoptosis and increased HPMC death in the same way as conventional PD solutions, but biocompatible PD solutions (low content GDPs, double chambered PD solutions) maintains low apoptosis levels as controls (Santamaria, B. et al. 2008)`79]. Mesothelial cells also die by apoptosis during peritonitis due to the combination of high levels of lethal cytokines and bioincompatible PD solutions as demonstrated in an experimental mice model of *S. aureus* peritonitis and following the intraperitoneal administration of inflammatory cytokines (Santamaria, B. et al. 2009)

Regarding the clinical evidence on the biocompatibility of glucose-based PD solutions (table 1), there is information from non-randomized observations and from clinical trials.

A retrospective observational study compared outcomes for 1100 incident CAPD patients treated with a single chamber peritoneal dialysis fluid (PDF) to the outcomes for patients treated with a low GDP double chamber PDF. Patients treated with Balance had significantly superior survival compared to those treated with the standard PDF (74% vs 62% at 28 months, p = 0.0032). This study was not stratified by age, the high number of patients with standard PDF and the absence of parameters like RRF, dialysis adequacy, transport status that are more related with survival (Lee, H. Y. et al. 2005).

A prospective non-randomized study of incident patients compared a conventional lactate solution (lactate group) to a pure bicarbonate solution (bicarbonate group) PD solution in 100 patients followed for three years in both groups (Montenegro, J. et al. 2007). The peritonitis rate was lower in patients treated with the pure bicarbonate solution than patients treated with the standard bioincompatible solution: 1 episode for each 36 patient-months versus 1 episode every 21 patient-months. At the end of the study, the RRF was significantly better preserved in patients of the bicarbonate group. Patients treated with pure bicarbonate ate more proteins according to normalized protein catabolic rate calculations and had lower markers of inflammation such as C reactive protein. Even mortality was lower in the bicarbonate group, even though this group had a higher Charlson index.

Several randomized controlled trials have focused mainly on preservation of RRF.

A crossover study compared the impact of a 25 mmol/L bicarbonate/15 mmol/L lactate buffered, solution (Physioneal) with a standard single chamber solution (Dianeal) (Fang, W. et al. 2008) on peritoneal transport and ultrafiltration. The mass transfer area coefficients (urea and creatinine) for both solutions did not differ. However net ultrafiltration was lower for Bic/Lac solution (274 ± 223 mL vs 366 ± 217 mL, p = 0.026). Physioneal avoided intraperitoneal acidity, which is present for up to 120 minutes with conventional acidic lactate solution.

The Euro-Balance trial with a crossover design and parallel arms, compared a single chamber conventional glucose-containing fluid with a lactate-buffered, low GDP double chamber glucose-containing fluid (balance) (Williams, J. D. et al. 2004). Clinical end points were RRF, adequacy of dialysis, ultrafiltration and peritoneal membrane function. Balance resulted in significantly higher effluent levels of CA125 and procollagen peptide in both arms of the study. Conversely, levels of Hialuronic acid were lower in patients exposed to balance, while there was no change in the levels of either VEGF or TNFa. Urine volume was higher in patients exposed to balance. In contrast, peritoneal ultrafiltration was higher in patients on conventional fluids. Increased extracellular volume and lower ultrafiltration in the patients with biocompatible solutions may be conditioning the results. The follow-up was short and changes in the RRF were a secondary objective.

A trial of incident patients starting PD examined changes in RRF (assessed by 24-h urine collection) over a1-year follow-up (Fan, S. L. et al. 2008). No differences were found between groups, for RRF, peritonitis rate, PD technique survival, changes in peritoneal membrane function assessed by peritoneal equilibrium test or C-reactive protein. Issues criticized in this study include the lack of statistical power to establish non inferiority as the difference of less than 1 ml / min in the RRF, use of solutions with different GDP content, inclusion of previous hemodialysis patients with little RRF and assessment of RRF at only two time points.

In 2009 three trials were published showing the benefit of biocompatible solutions in regard to RRF, ultrafiltration and tolerability.

A study of 91 incident CAPD patients for 12 months compared neutral-pH and low GDP (Balance) and conventional solutions (Kim, S. et al. 2009). Biocompatible solution preserved RRF compared with conventional solutions (p=0.048). Analysis by subgroups (GFR>2 ml/min) demonstrated the preservation of RRF in per protocol analysis.

In a crossover study with 26 prevalent patients treated for 3 months with lactate-based and 3 months with bicarbonate/lactate-based solution (Pajek, J. et al. 2009), switch from conventional solutions to biocompatible solution decreased ultrafiltration (p=0.012) and switch from biocompatible to conventional solution increased ultrafiltration solutions (p=0.001).

A cross over multicenter trial (Weiss, L. et al. 2009) enrolled 53 patients and compared conventional vs Bicarbonate PD fluid. Patients with biocompatible solutions had a higher concentration of CA125 (p<0.001) and less concentration of hyaluronic acid (p=0.013), TNF-α (p<0.001) and TGF-β1 (p=0.016). These biocompatibility markers suggest improvement in peritoneal membrane integrity In addition, a positive effect on RRF was observed (p=0.011).

Drawbacks. Biocompatible, glucose-containing PD solutions maintain the adverse effects of glucose itself.

In addition, a surprising effect of ultrafiltration has been observed that was not anticipated by experimental studies in animals. Biocompatible, glucose-containing PD solutions buffered with lactate or bicarbonate decrease ultrafiltration compared to conventional solutions in some patients: In some cases this is related to increased peritoneal transport of small molecules (Williams, J. D. et al. 2004). This effect is acute (observable with a single exchange) and reversible by discontinuing the solution. Furthermore, the decreased ultrafiltration observed with biocompatible glucose-containing PD solutions is not indicative of peritoneal injury and in this, it differs from the progressive increase in solute permeability observed over the years in PD as a result of peritoneal injury induced by conventional solutions. The results obtained when assessing the impact of lactate/bicarbonate-buffered PD solutions have not been consistent. However, a recent study showed a decrease in ultrafiltration compared to conventional solutions when compared in the same patient in a short period of time (Fang, W. et al. 2008). The interest in learning about differences in the behavior of the various solutions lies in a better understanding of the cause of these differences, which could be related to differences in pH, buffer or GDP content. A recently reported very low GDPs solution, with physiological pH and buffered with bicarbonate / lactate increased ultrafitración against a similar solution containing GDPs, pH 6.3 and lactate (Simonsen, O. et al. 2006).

An additional caveat should be made. In some patients bicarbonate-buffered solutions can overcorrect the metabolic acidosis of uremia, causing metabolic alkalosis (Vande Walle, J. G. et al. 2004; Garcia-Lopez, E. et al. 2005; Otte, K. et al. 2003).

5.2 Alternative osmotic agents
Icodextrin and amino acids are the only alternative to glucose agents that are commercially available.

5.2.1 Icodextrin
Polyglucose or icodextrin is a carbohydrate of high molecular weight obtained by hydrolysis of corn starch (Figure 3) (Frampton, J. E. et al. 2003). Icodextrin consists of a mixture of glucose polymers of different sizes (from 2 to 300 molecules of glucose) with a total average molecular weight of 13 to 19 KDa and average molecular weight per molecule of 5 to 6.5 KDa (range 0.36-54). Icodextrin is available commercially at a concentration of 7.5%.

However, icodextrin cannot be strictly considered a biocompatible solution, due to the intrinsic problems of the glucose polymer, such as generation high levels of circulating maltose in the systemic circulation. In this regard, no more than one exchange a day can be prescribed according to heath authorities.

Fig. 3. Schematic representation of molecules of glucose, maltose, icodextrin polymers and intermediates.

Advantages and indications. Icodextrin-containing solutions are isosmolar and induce ultrafiltration by oncotic pressure. Icodextrin is absorbed by lymphatic vessels, more slowly than glucose. As a consequence, the oncotic pressure is durable and ultrafiltration is linear and more sustained than that induced by glucose. During an exchange of 10-16 hours 40% of icodextrin in an exchange is absorbed (Garcia-Lopez, E. et al. 2005; Moberly, J. B. et al. 2002). These features suggest the following icodextrin indications:

a. Long daytime exchange in APD (as the last cycler infusion) or the night dwell during CAPD in order to increase ultrafiltration and sodium removal (Davies, S. J. et al. 2005; Rodriguez-Carmona, A. et al. 2002; Davies, S. J. et al. 2008). In randomized controlled trials icodextrin improved the hydration status of patients ((Davies, S. J. et al. 2008; Wolfson, M. et al. 2002; Plum, J. et al. 2002). Icodextrin allows greater ultrafiltration in long exchanges than solutions with 1.5% or 2.3% glucose. Furthermore, icodextrin allows greater ultrafiltration in long exchanges than 4.25% glucose in high transporters. Since icodextrin is not a small molecule, ultrafiltration may be obtained with icodextrin in patients with failure of ultrafiltration due to high transport of small solutes. The ability to obtain ultrafiltration in these patients can prolong the life of the PD technique, delaying the transition to hemodialysis. More ultrafiltration allows a greater clearance of molecules when comparing a prolonged exchange (approx. 12 hours) of icodextrin with a glucose exchange of the same duration, especially if the concentration of glucose is 1.5% (Wolfson, M. et al. 2002). However, solute clearance is less with a long exchange of icodextrin than with two shorter glucose exchanges (approx 6 hours per glucose exchange).

b. Limit exposure to high concentrations of glucose and GDPs and absorption of glucose. This can help to preserve the functionality of the peritoneal membrane (Davies, S. J. et al. 2005). Although there are few differences in the absorption of the total amount of carbohydrates, icodextrin prevents the absorption peaks of glucose. This may contribute to less weight gain, lipid abnormalities and improved glycemic control and HbA1c levels in poorly controlled diabetic patients (Wolfson, M. et al. 2002; Babazono, T. et al. 2007).

c. Maintenance of ultrafiltration during episodes of peritonitis since the ultrafiltration capacity of icodextrin solutions is independent of peritoneal permeability to small solutes.

Peculiarities. Amylase degrades icodextrin, but in humans there is little amylase in the peritoneal cavity (unlike in some rodents). Absorbed icodextrin is degraded by circulating amylase. The consequences of icodextrin degradation by circulating amylase may be summarized as follows:

a.   Increased plasma concentration of maltose (maltose 20-300 times increased over physiological levels to 120 mg/dl or 3 mM, compared to physiological glucose concentrations from 3.3 to 5.5 mM), maltotriose and other glucose polymers (Garcia-Lopez, E. et al. 2005; Burkart, J.2004; Posthuma, N. et al. 1997). These metabolites are normally excreted in the urine or degraded to glucose by tissue maltase tissue. The richest tissue in maltase is the kidney. In renal failure these two mechanisms of elimination fail, facilitating maltose accumulation. This risk of maltose accumulation limits the use of icodextrin to a single exchange within a 24 hour period. So far, no toxic effects have been identified resulting from accumulation of maltose when icodextrin is used according to the prescription data sheet.

b.   Maltose and other oligosaccharides that accumulate in the blood of patients treated with icodextrin interfere with some plasma glucose monitors and test strips readings, resulting in falsely elevated glucose readings (Wang, R. et al. 2004; Wens, R. et al. 1998). In patients treated with icodextrin only glucose monitors and test strips that use glucose-specific methods should be used. These include methods based on glucose oxidase (GO), hexokinase, glucose dehydrogenase nicotine adenine dinucleotide (GDH-NAD), or glucose dehydrogenase with flavin adenine dinucleotide (GDH-FAD). Methods not to be used include glucose dehydrogenase pirrolquinolinaquinone (GDH-PQQ) or glucose-dye-oxidoreductase, which detect both glucose and maltose. After stopping the use of icodextrin it takes around 14 days for the plasma levels of icodextrin and its metabolites to return to undetectable (Plum, J. et al. 2002).

c.   Mild decline in serum sodium without hypo-osmolarity to values around 135-137 mmol / L. This is associated with an increased osmolal gap due to the presence of circulating metabolites of icodextrin (which justify an increase in osmolal gap of about 8 mOsm / kg) (Plum, J. et al. 2002; Posthuma, N. et al. 1997).

d.   Decrease in measured plasma amylase levels, because the circulating metabolites of icodextrin interfere with the assay (Plum, J. et al. 2002). So if pancreatitis is suspected, lipase should be assayed.

Adverse effects. The most common side effect of icodextrin in clinical trials was skin hypersensitivity (2.5-5% of exposed individuals), which usually occurs in the first 3 weeks and require discontinuation of treatment, although in some patients the rash disappears despite continued use of icodextrin (Frampton, J. E. et al. 2003; Wolfson, M. et al. 2002).

In the late 90s and early 2000s there was an epidemic of sterile peritonitis in patients treated with icodextrin. The cause was contamination of some lots with peptidoglycan, a component of the wall of gram-positive bacteria (Goffin, E. et al. 2003). New control systems of production have largely eliminated the problem and no influence has been observed of icodextrin on peritonitis incidence rates, either culture positive or negative (Vychytil, A. et al. 2008).

5.2.2 Amino acids

PD solutions containing amino acid solutions can limit the use of glucose. In addition, amino acids provide nutritional components (Tjiong, H. L. et al. 2005). The only marketed solution contains 1.1% amino acids, equivalent to an amino acid concentration of 87 mM / L (Table 6). The average molecular weight of the amino acids is 126. Approximately 65% of

them (15 g/exchange) are absorbed into the systemic circulation during a 4-6h PD exchange. This is enough to replace the approximately 5-8 g/day of protein and 3 g/day of amino acids that are lost in non-aminoacid PD exchanges (Rippe, B. et al. 2007). The osmotic power of the amino acid solutions is comparable to a solution of 1.5% glucose. The osmolarity is slightly higher than the 1.5% glucose solution and a slightly higher ultrafiltration has been reported, approximately 100 ml at 4 h, despite a greater absorption of the osmotic agent. The increased uptake is probably due to the lower average molecular weight of the amino acids and to amino acid-induced vasodilation (Rippe, B. et al. 2007; Olszowska, A. et al. 2007).

Aminoacid	Concentration (mM/L)
L-Valine	11.88
L-Alanine	10.67
L-Leucine	7.79
Glycine	6.80
L-Lysine, HCl	6.51
L-Isoleucine	6.49
L-Arginine	6.15
L-Methionine	5.70
L-Threonine	5.46
L-Proline	5.13
L-Serine	4.86
L-Histidine	4.58
L-Phenylalanine	3.45
L-Tyrosine	1.66
L-Tryptophan	1.32

Table 6. Aminoacid concentration in the only commercially available aminoacid PD solution

Advantages and indications. The use of amino acids as osmotic agents decreases peritoneal glucose load and glucose uptake from the peritoneal cavity. This is especially relevant in diabetic and obese individuals. Amino acid solutions also are moderately effective as a nutritional supplement in malnourished patients. In short-term studies protein synthesis improved when amino acid solutions were associated with an adequate supply of calories, such as oral intake or by combining aminoacids with glucose in cycler (Garibotto, G. et al. 2001; Tjiong, H. L. et al. 2005; Tjiong, H. L. et al. 2007). The effect tends to be less consistent in the long-term, probably because other factors influence serum albumin such as inflammation, acidosis or inadequate calorie intake (Kopple, J. D. et al. 1995). However, in a 3-year study malnourished patients using 1.1% amino acids better maintained serum albumin (Li, F. K. et al. 2003). A decrease of serum phosphorus has also been reported and attributed to the contribution of amino acids in the absence of phosphate (Kopple, J. D. et al. 1995). In this sense, the same amount of amino acid if ingested orally, is associated with approximately 300 mg of phosphate.

Drawbacks. Amino acid solutions can only be used once daily since a higher number of bags favors acidosis (which can be compensated by oral treatment with bases or PD solutions with higher buffer content) and increases urea (Tjiong, H. L. et al. 2007; Kopple, J. D. et al. 1995; le Poole, C. Y. et al. 2005). The tendency to acidosis and uremia is more

pronounced in catabolic patients, so factors that promote catabolism should be corrected and an adequate calorie intake should be maintained to prevent the catabolism of amino acids as an energy source. This can be achieved with oral caloric intake or by mixing amino acid containing PD solutions with glucose solutions simultaneously in the cycler exchanges. In addition, the methionine load from the dialysate may significantly increase plasma homocysteine levels, especially in patients with lower protein and methionine intakes (Yang, S. Y. et al. 2005). Increased plasma homocysteine levels have been associated with impaired cardiovascular outcomes. In this regard, one 6-h dwell with a commercial amino acid dialysis solution acutely impaired forearm reactive hyperemia, a marker of endothelial dysfunction, in smoking and nonsmoking PD patients (Vychytil, A. et al. 2003).
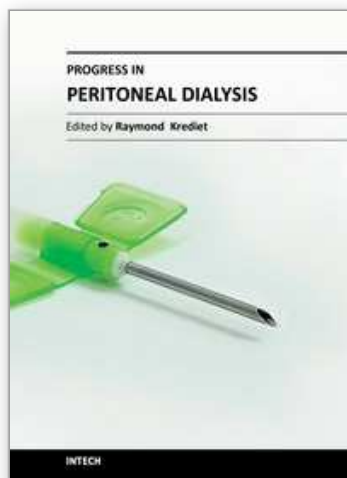
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