A NEW NEUTRAL-pH LOW-GDP PERITONEAL DIALYSIS FLUID

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◆ **Background:** Conventional peritoneal dialysis fluids (PDFs) consist of ready-to-use solutions with an acidic pH. Sterilization of these fluids is known to generate high levels of glucose degradation products (GDPs). Although several neutral-pH, low-GDP PD solutions have been developed, none are commercially available in the United States. We analyzed pH and GDPs in Delflex Neutral pH (Fresenius Medical Care North America, Waltham, MA, USA), the first neutral-pH PDF to be approved by the US Food and Drug Administration.

◆ **Methods:** We evaluated whether patients ($n = 26$; age range: 18 – 78 years) could properly mix the Delflex Neutral pH PDF after standardized initial training. We further analyzed the concentrations of 10 different glucose degradation products in Delflex Neutral pH PDF and compared the results with similar analyses in other commercially available biocompatible PDFs.

◆ **Results:** All pH measurements ($n = 288$) in the delivered Delflex Neutral pH solution consistently fell within the labeled range of 7.0 ± 0.4 . Analysis of mixing errors showed no significant impact on the pH results. Delflex Neutral pH, Balance (Fresenius Medical Care, Bad Homburg, Germany), BicaVera (Fresenius Medical Care), and Gambrosol Trio (Gambro Lundia AB, Lund, Sweden) exhibited similar low total GDP concentrations, with maximums in the 4.25% solutions of $88 \mu\text{mol/L}$, $74 \mu\text{mol/L}$, $74 \mu\text{mol/L}$, and $79 \mu\text{mol/L}$ respectively; the concentration in Physioneal (Baxter Healthcare Corporation, Deerfield, IL, USA) was considerably higher at $263.26 \mu\text{mol/L}$. The total GDP concentration in Extraneal (Baxter Healthcare Corporation) was $63 \mu\text{mol/L}$, being thus slightly lower than the concentrations in the 4.25% glucose solutions, but higher than the concentrations in the 1.5% and 2.5% glucose solutions.

◆ **Conclusions:** The new Delflex Neutral pH PDF consistently delivers neutral pH with minimal GDPs.

KEY WORDS: Biocompatible dialysis solutions; neutral pH; glucose degradation products; biocompatibility.

Conventional peritoneal dialysis fluids (PDFs) are ready-to-use solutions with an acidic pH presented in a single-chamber bag with glucose as the osmotic agent. Heat sterilization or extended storage of these solutions leads to the formation of bioincompatible glucose degradation products (GDPs), which are important catalysts for the formation of advanced glycation endproducts (AGEs).

The foregoing factors—pH, GDPs, and AGEs—directly affect the biocompatibility of PDFs, as defined by the ability of a biomaterial to function without undesirable local or systemic effects, but with an appropriate beneficial cellular or tissue response and optimal clinically relevant performance of the therapy (1,2). Those factors therefore meet the definition of bioincompatibility as proposed by some authors, which could be a result of low pH (3,4) or of high GDPs (5–10). The relevance and toxicity of GDPs have been demonstrated to be independent from those of glucose. Importantly, Igaki *et al.* demonstrated that the GDP 3-deoxyglucosone (3-DG), and not glucose, accelerates the advanced stage of protein glycation (11).

Several investigators have analyzed methods for reducing GDP content and improving the biocompatibility of PDFs. Wieslander *et al.* suggested that separation of the dextrose and buffer components during storage or heat sterilization could reduce GDP formation (12,13). Kjellstrand *et al.* showed that sterilization of glucose at an optimal pH (approximately 3) minimizes GDP formation in glucose-containing solutions (10). Erixon *et al.* confirmed that sterilization of glucose at a pH between 2.0 and 2.6 significantly reduced levels of 3-DG, 5-hydroxymethylfuraldehyde (5-HMF), and 3,4-dideoxyglucosone-3-ene (3,4-DGE), the most bioactive and cytotoxic of the GDPs (14–17) present within available PDFs (18). Further separation of the buffer solution from the dextrose almost entirely eliminated the production of

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the GDP acetaldehyde (AcA) (19–21). Moreover, storage of the dextrose component at a pH below 4.0 has been shown to substantially reduce GDP formation (22).

Within the past few years, several low-GDP PDFs, featuring a double-chamber bag that allows for sterilization and storage of the glucose at a low pH, have become commercially available. The beneficial effects on cell viability and peritoneal host defenses of a neutral pH combined with a low concentration of GDPs are abundantly documented in the literature (23), but a PDF with those properties is not yet available in the United States.

In the present paper, we introduce the first neutral-pH PDF that has been approved by the US Food and Drug Administration (FDA), Delflex Neutral pH (Fresenius Medical Care North America, Waltham, MA, USA), and we compare it with commercially available low-GDP PDFs in other countries. The new Delflex Neutral pH, a solution that has been optimized for low GDPs, features a new bag design and delivery system that combines a single-chamber bag for the main solution (containing dextrose, sodium chloride, calcium, and magnesium) with a unique external second compartment (containing lactate and bicarbonate) linked through a mechanical interlock system that prevents outflow unless the solutions are mixed (Figure 1).

METHODS

Analysis of mixing efficacy and resultant pH and evaluation of mixing feasibility by patients and nurses were performed only for the Delflex Neutral pH PDF, because it features a unique new bag design and delivery system. All other solutions are well established in the market and

Figure 1 — The new bag design and delivery system of Delflex Neutral pH (Fresenius Medical Care North America, Waltham, MA, USA) combines a single-chamber bag for the main solution (containing dextrose, sodium chloride, calcium, and magnesium) with a small external second compartment (containing lactate and bicarbonate) linked through a mechanical interlock system that prevents outflow unless the solutions are mixed. PD = peritoneal dialysis.

have been proven to yield safe mixing results in clinical practice. For the quantification of GDPs, all solutions were analyzed according to the standards and methods outlined later in this section.

MIXING EFFICACY

To evaluate proper mixing of the acid and alkaline solutions from the two compartments of Delflex Neutral pH PDF, we measured the pH of the mixed solution after patient training. We also analyzed the potential effects of mixing errors on the results. Tests were performed in 26 patients 18 – 78 years of age (average age: 51.4 years), who were chosen from 3 different clinics across the continental United States. Participants were current home users of Fresenius Stay•Safe PDF for automated peritoneal dialysis (PD) or continuous ambulatory PD.

PATIENT AND NURSE TRAINING

Patients were trained in their local clinic by a PD nurse on the day that they performed the mixing of the product. All participants gave written informed consent before participation in the study. Training materials used by nurses and patients included the Delflex Neutral pH PDF, the instructions-for-use card, and a Delflex Neutral pH procedure card with step-by-step color photos. Patient training consisted of a demonstration by a PD nurse with the actual product, a reading of the instructions-for-use card, and use of the illustrated procedure card. The maximum patient-to-trainer ratio was 3:1. After training, participants moved to individual treatment rooms to initiate and complete 4 simulated-use treatments. Patients were not allowed to receive any guidance or instruction from the nurse on product use during the mixing. Each patient completed 4 independent uses of the product under nurse supervision and was monitored for procedural errors and to ensure that the product was discarded and not infused into the intraperitoneal cavity.

pH OUTFLOW SAMPLING

The PDF was sampled at 3 stages during simulated infusion (the patients did not actually infuse the solution) to assess mixing efficacy. Sample volumes of 200 mL were collected at 0% (first), 45% (middle), and 90% (last) dispensed volume. These sampling points were selected to observe the product pH at points where deviations from the nominal pH were most likely to occur. Aliquots were withdrawn from the transfer line at the specified stages and dispensed into sealed containers for pH measurement.

pH ANALYSIS

The pH of samples was tested using a Mettler Toledo (Columbus, OH, USA) SevenMulti pH meter equipped with a pH/mV expansion module and InLab Routine Pro electrode with automatic temperature correction. The pH probes were calibrated in segmented mode using buffers of pH 2, 4, 7, and 10. Probe calibration was verified using pH 6.0 and 7.4 standards, and the probes were monitored for drift thereafter. If the probe calibration drifted in excess of 0.02 pH units from the specified nominal standard value, the probe was recalibrated. The probe was placed in the sample container together with a Teflon-coated stir bar, and the sample was gently stirred for 60 s before the pH measurement was taken.

EVALUATION SURVEY

Nurses and patients were asked to complete a survey consisting of 6 questions with a rating scale of 1 – 5 (1 = worst, 5 = best). Scores are given as mean values.

QUANTIFICATION OF GDPs

Levels of formaldehyde (FoA), AcA, 5-HMF, 2-furaldehyde, and methylglyoxal (MGLx) were measured at the Fresenius Medical Care laboratory in St. Wendel, Germany. Levels of the remaining degradation products [glucosone; 3,4-DGE; glyoxal (GLx); 3-DG; and 3-deoxygalactosone (3-DGal)] were measured in a collaborator's laboratory at the University of Erlangen, Germany. A subset of the GDP measurements presented in this paper was used to establish and validate the quantification method as previously published by Frischmann and coworkers (24).

A reliable method to identify 3-DGal has only recently been established (25). Earlier publications measured total 3-DG levels, representing cumulative values for 3-DG and 3-DGal. Therefore, to accurately compare the present results with those for other products [for example, Balance (Fresenius Medical Care, Bad Homburg, Germany), BicaVera (Fresenius Medical Care), and others], the 3-DG and 3-DGal content in Delflex Neutral pH bags is shown as a combined "3DG+3DGal" value where appropriate.

In each case, the samples were derivatized and allowed to react with *o*-phenylene diamine to yield an ultraviolet-detectable molecule before measurements were taken. The measurements were taken with a high-performance liquid chromatography device equipped with an ultraviolet detector, as previously described (24), or using ultrahigh-performance liquid chromatography

in combination with an ultraviolet detector (25). Table 1 shows the limits of quantification (different for each molecule). Figure 2 shows the chemical structures of the measured GDPs.

ANALYZED PDFS

We analyzed the GDP content of the new Delflex Neutral pH PDF and of a comprehensive set of biocompatible solutions with reduced GDP content, including Balance, BicaVera, Gambrosol Trio (Gambro Lundia AB, Lund, Sweden), and Physioneal and Extraneal (Baxter

TABLE 1
Quantification Limits for Individual Glucose Degradation Products (GDPs)

GDP	Limit	
	Lower	Upper
Glucosone	0.56 $\mu\text{mol/L}$	0.10 mg/L
3-Deoxyglucosone	0.56 $\mu\text{mol/L}$	0.09 mg/L
3-Deoxygalactosone	0.49 $\mu\text{mol/L}$	0.08 mg/L
3,4-Dideoxyglucosone-3-ene	0.42 $\mu\text{mol/L}$	0.06 mg/L
Glyoxal	0.52 $\mu\text{mol/L}$	0.03 mg/L
Formaldehyde	3.33 $\mu\text{mol/L}$	0.10 mg/L
Acetaldehyde	2.27 $\mu\text{mol/L}$	0.10 mg/L
5-HMF	0.77 $\mu\text{mol/L}$	0.10 mg/L
2-Furaldehyde	1.04 $\mu\text{mol/L}$	0.10 mg/L
Methylglyoxal	1.39 $\mu\text{mol/L}$	0.10 mg/L

Figure 2 — Structures of the measured glucose degradation products (GDPs). 3-Deoxygalactosone (3-DGal) is the C4 epimer of 3-deoxyglucosone (3-DG). That is, the hydroxyl group at position 4 in the 3-DGal molecule is positionally stereoisomeric to 3-DG.

Healthcare Corporation, Deerfield, IL, USA). Table 2 sets out the characteristics of the solutions. To obtain statistically sound results, the GDP analysis included at least 3 batches per product type and glucose strength, as available in Germany, and four bags per batch were analyzed in duplicate.

STATISTICS

All GDP variables were measured in triplicate. The results are expressed as means and standard deviations. More in-depth statistical analyses were performed during optimization of the measurement procedure, and those analyses are published elsewhere (24,25). For pH measurements, 95% confidence intervals (CIs) were calculated. Distribution of the datasets used for determining mixing errors was assessed using a Shapiro-Wilks W-test at a confidence level of 95%. A two-sample t-test was used to determine the significance of differences of means. Statistical significance was defined as $p < 0.05$.

RESULTS

DELIVERED pH

To assess mixing efficacy and consistency during the various stages of delivery, 3 samples were taken for pH measurements during each exchange for each patient. These samples were taken at stages where deviations from the nominal pH were most likely to occur.

Figure 3 shows the pH measurements for 96 exchanges (a total of 288 pH measurements). First (0% dispensed volume), middle (45% dispensed volume), and last (90% dispensed volume) pH samples are represented. All pH data collected fell within the labeled range for the Delflex Neutral pH PDF: 7.0 ± 0.4 . Of all measurements, 2 reached a minimum and maximum nominal pH of 6.6 and 7.4 respectively; the remaining 286 measurements were within the 6.7 – 7.1 range. The results from the first pH dataset (0% dispensed) were normally

Figure 3 — The pH in delivered peritoneal dialysis fluid. A total of 288 pH measurements (3 pH measurements each for 96 simulated exchanges) are shown. First, middle, and last pH samples are represented by green, blue, and red dots respectively. The product specification limits are indicated at pH values of 6.60 and 7.40. The mean pH measured for the product during testing was 6.820 ($n = 5$). All pH data collected fell within the product specification limits of 7.0 ± 0.4 .

TABLE 2
Characteristics of Measured Peritoneal Dialysis Solutions

Solution	Osmotic agent	Strengths (%) ^a	Buffer (mmol/L)	pH
Delflex ^b				
Conventional	Glucose	1.5, 2.5, 4.25	Lactate (35 or 40)	~5.5
Neutral pH	Glucose	1.5, 2.5, 4.25	Lactate (35 ^c)	7.0
Balance ^d	Glucose	1.5, 2.5, 4.25	Lactate (35 ^c)	7.0
BicaVera ^d	Glucose	1.5, 2.5, 4.25	Bicarbonate (34 or 39)	7.4
Gambrosol Trio ^e	Glucose	1.5, 2.5, 3.9	Lactate (40)	5.5–6.5
Physioneal ^f	Glucose	1.5, 2.5, 4.25	Lactate (10 or 15) and bicarbonate (25)	7.4
Extraneal (icodextrin) ^f	Polyglucose	7.5	Lactate (40)	5.0–6.0

^a All values are expressed as hydrous glucose.

^b Fresenius Medical Care North America, Waltham, MA, USA.

^c Contains ≤ 3.5 mmol/L bicarbonate for pH adjustment.

^d Fresenius Medical Care, Bad Homburg, Germany.

^e Gambro Lundia AB, Lund, Sweden.

^f Baxter Healthcare Corporation, Deerfield, IL, USA.

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distributed (mean pH: 6.84; 95% CI: 6.74 to 6.93). The intermediate and final datasets (at 45% and 90% of dispensed solution) had narrower distributions, but similar medians.

PATIENT ERRORS DURING MIXING

During the exchange procedure, patients were monitored for the occurrence of major and minor errors. "Major errors" were mixing errors by patients that could potentially affect the pH of the final product. "Minor errors" were mixing errors that should not significantly affect the final delivered pH of the solution.

In total, 41 minor and 13 major errors were observed. On average, 15 minor errors were noted during the first exchange; that number declined with each subsequent exchange to 6 minor errors during the fourth and final exchange. The average number of major errors was 3, 1, 6, and 3 errors in the first, second, third, and fourth exchanges respectively. To determine how mixing procedure errors affected the pH results in the ready-to-use solutions, a comparison was made between the 60 exchanges that were free of any mixing errors and the 13 exchanges that were associated with major errors. The mean pH values for the error-free and major-error groups were 6.835 (95% CI: 6.730 to 6.936) and 6.839 (95% CI: 6.754 to 6.925) respectively. For both datasets, the Shapiro-Wilks W-test determined that there was no significant departure from normality. A two-sample t-test for the difference of means concluded that the mean of the "error" group was not significantly different from the mean of the "no-error" group at the 95% confidence level. The data show that, despite errors in mixing, the pH and homogeneity of the final solution were not compromised.

Figure 4 — Evaluation survey. Patients and nurses were asked 6 questions. Average responses are shown. Scores were rated from 1 to 5, where 1 = worst and 5 = best.

EVALUATION SURVEY

Survey results (Figure 4) suggested that nurses and patients found the product easy to learn, set up, and use. The rating for every question was 3 or more, with a median of 5 for each question. The total average for all 5 ratings questions, for all participants, was 4.68 out of 5 (standard deviation: 0.56). User feedback suggested that the product design is functional and effective. Patient and nurses indicated that, because of perceived health benefits, they would use the product if it were available on the market.

MEASUREMENT OF GDPs IN THE DELFLEX NEUTRAL PH SOLUTIONS

We analyzed the concentrations of 10 GDPs in the new Delflex Neutral pH PDFs. Table 3 sets out the data for each GDP. The values for 2-furaldehyde and MGxl were below the detection limits. The average total GDP content was 33.17 $\mu\text{mol/L}$, 57.44 $\mu\text{mol/L}$, and 88.84 $\mu\text{mol/L}$ in the 1.5%, 2.5%, and 4.25% solution respectively.

COMPARISON OF GDP LEVELS IN COMMERCIALY AVAILABLE LOW-GDP SOLUTIONS

Figures 5 – 7 show the mono- and dicarbonyl GDP content of Delflex Neutral pH PDF compared with that in various commercially available low-GDP solutions. A subset of those data was previously published (26).

TABLE 3
Concentrations^a of the Individual Glucose Degradation Products (GDPs) Measured in Delflex Neutral pH^b Solutions

GDP	Solution with a glucose concentration of		
	1.50%	2.50%	4.25%
Formaldehyde	0	0	3.56
Acetaldehyde	2.42	2.57	2.52
5-HMF	6.18	12.21	20.15
Glucosone	3.13	8.51	13.12
3,4-DGE	0.86	0.69	1.33
Glyoxal	1.41	4.21	5.57
3-DG	10.58	18.24	30.53
3-DGal	4.85	8.2	13.94
TOTAL	33.17	57.44	88.44

5-HMF = 5-hydroxymethylfuraldehyde; 3,4-DGE = 3,4-dideoxyglucosone-3-ene; 3-DG = 3-deoxyglucosone; 3-DGal = 3-deoxygalactosone.

^a Mean of triplicate measurements in millimoles per liter.

^b Fresenius Medical Care North America, Waltham, MA, USA.

Figure 5 — Comparison of the monocarbonyl glucose degradation product (GDP) content in Delflex Neutral pH (Fresenius Medical Care North America, Waltham, MA, USA) with that in other biocompatible solutions. Balance, BicaVera: Fresenius Medical Care, Bad Homburg, Germany. Gambrosol Trio: Gambro Lundia AB, Lund, Sweden. Physioneal, Extraneal: Baxter Healthcare Corporation, Deerfield, IL, USA.

Figure 6 — Comparison of the dicarbonyl glucose degradation product (GDP) content in Delflex Neutral pH (Fresenius Medical Care North America, Waltham, MA, USA) with that in other biocompatible solutions. Balance, BicaVera: Fresenius Medical Care, Bad Homburg, Germany. Gambrosol Trio: Gambro Lundia AB, Lund, Sweden. Physioneal, Extraneal: Baxter Healthcare Corporation, Deerfield, IL, USA.

For the monocarbonyl GDPs (Figure 5), the largest variations in solution GDP content were observed for 5-HMF and AcA. The GDP most affected by glucose concentration appears to be 5-HMF, with the highest values seen in Physioneal. The concentration of AcA was markedly higher in Extraneal than in any of the glucose-based solutions. The concentration of FoA did not vary between the various solutions. The concentration of 2-furaldehyde was found to be similar in all solutions, except for a higher concentration in Physioneal.

Figure 7 — Comparison of the total glucose degradation product (GDP) content in Delflex Neutral pH (Fresenius Medical Care North America, Waltham, MA, USA) with that in other biocompatible solutions. Balance, BicaVera: Fresenius Medical Care, Bad Homburg, Germany. Gambrosol Trio: Gambro Lundia AB, Lund, Sweden. Physioneal, Extraneal: Baxter Healthcare Corporation, Deerfield, IL, USA.

Figure 6 shows the concentration of the dicarbonyl GDPs in the various solutions. The Delflex Neutral pH PDFs contained concentrations of dicarbonyl GDPs that were comparable to those in the Balance, BicaVera, and Gambrosol Trio PDFs. By contrast, Physioneal showed markedly higher concentrations of 3,4-DGE, glucosone, and 3DG+3DGAL. The 3DG+3DGAL component was the highest in all solutions except for Extraneal, in which glucosone was the most prevalent GDP.

Figure 7 shows the total GDP content as the sum of the individual GDP concentrations. Delflex Neutral pH, Balance, BicaVera, and Gambrosol Trio showed similar low total GDP concentrations; the maximum concentrations were 88 µmol/L, 74 µmol/L, 74 µmol/L, and 79 µmol/L respectively in the 4.25% solutions. The maximum concentration in Physioneal was considerably higher at 263.26 µmol/L. The total concentration of GDPs in Extraneal was 63 µmol/L, and thus slightly lower than the concentrations in the other 4.25% glucose PDFs, but higher than the concentrations in the 1.5% and 2.5% glucose PDFs. Moreover, compared with the two-chamber glucose PDFs, Extraneal additionally showed a different GDP distribution pattern.

DISCUSSION

Here, we introduce the first FDA-approved, neutral-pH, biocompatible PD solution with a low GDP content—Delflex Neutral pH. We also demonstrate that patients can easily learn to use this new solution, obtaining a physiologically appropriate pH after mixing.

The Delflex Neutral pH PDF is formulated to provide a neutral pH of 7.0 ± 0.4 , which comes closer to physiologic pH than conventional PDFs do. Our mixing results showed that, of 288 pH measurements, including those with mixing errors, all were within the nominal pH. Compared with other low-GDP solutions on the market, the Delflex Neutral pH PDFs, with their pH of 7.0 ± 0.4 , are similar to the Balance, BicaVera, and Physioneal PDFs. Gambrosol Trio and Extraneal have acidic pHs of 5.5 – 6.5 and 5.0 – 6.0 respectively.

The data presented here demonstrate that patients made fewer minor errors as they performed more exchanges, indicating a learning effect. However, a similar trend was not seen for the observed major errors, possibly because of their low number. The positive pH results might have been partly attributable to the quality of the training and to the instructions for use provided to the participating nurses and patients, because the investigators meticulously tried to mirror the real-life situations of the patients as closely as possible. It could be argued that the results were biased by performing the exchanges within a study setting in which the patient might be more focused on the procedures. However, the learning effect seen within the 4 exchanges suggests that even better results can be expected as more experience is gained with the handling and mixing of the PD bags. Importantly, the design of the new Delflex Neutral pH bags incorporates a mechanical interlock system positioned between the compartments; outflow is prevented unless the solutions are mixed. A connection port is provided for dispensing the mixed neutral-pH solution for PD.

We previously determined that patients could easily be trained, within 2 hours, to use the new delivery system (26). The fact that a comparison of the pH results for the samples with and without major mixing errors showed a lack of any statistically significant differences further indicated that the design of the Delflex Neutral pH bag ensures a consistently delivered pH in the ready-to-use PD solution.

Although other neutral-pH biocompatible PDF formulations with low GDPs (such as Balance, BicaVera, and Physioneal) are commercially available in several markets, none are currently available in the United States (Table 2). Extraneal (polyglucose), although available in the United States, has low GDP content, but does not feature a neutral pH (24).

Our results illustrate that the new Delflex Neutral pH PDFs contain only a very small GDP concentration, well below $100 \mu\text{mol/L}$. Figure 8 compares the concentrations of the 6 most abundant GDPs in the Delflex Neutral pH solutions with previously published data on

GDP concentrations in conventional Delflex solutions (26). Depending on the glucose concentration, Delflex Neutral pH PDF showed an 86.9% – 92.1% reduction in total concentration of GDPs: 92.1% in the 1.5% solution, 89.7% in the 2.5%, and 86.9% in the 4.25%. Compared with conventional Delflex, Delflex Neutral pH showed a reduced concentration of 3-DG by at least 75%, and near total elimination of AcA, FoA, and MGxL. The remaining GDPs found in the Delflex Neutral pH bags were predominantly 5-HMF, 3-DG, 3-DGal, and glucosone. The Delflex Neutral pH PDF showed an expected increase in the 10 measured GDPs with increasing glucose concentration, but the relative distribution of GDPs did not change.

Erixon *et al.* (18), and later Frischmann *et al.* (24), showed that, among the commercially available biocompatible PDFs, GDP profiles vary considerably, particularly with respect to 3,4-DGE. We therefore compared the levels of GDPs—including FoA, AcA, 5-HMF, 2-furaldehyde, MGxL, glucosone, 3,4-DGE, GxL, 3-DG, and 3-DGal—in various commercially available PDFs with the corresponding levels in Delflex Neutral pH. Comparison of the glucose-based PDFs showed that four (that is, all except Physioneal) had an ultralow GDP content (below $100 \mu\text{mol/L}$) and showed a similar pattern of GDPs (Figures 5 – 7).

Physioneal was the only PDF with a considerable amount of 3,4-DGE, which is the most cytotoxic GDP known (15–17). Moreover, the total GDP content of Physioneal was several times higher than that found in the other solutions. The higher pH of the glucose compartment (4.0 – 4.2 compared with 3.0 in the Fresenius and Gambro products) might be a critical

Figure 8 — Concentration of glucose degradation products (GDPs) in conventional Delflex [Fresenius Medical Care North America, Waltham, MA, USA; previously published by Diaz-Buxo *et al.* (26)] and Delflex Neutral pH. The first three columns represent the conventional solutions, and the last three columns, Delflex Neutral pH.

contributing factor to the increased GDP formation during sterilization (21,22).

Extraneal was the only polyglucose-based solution tested; it showed an intermediate total GDP content when compared with the four ultralow-GDP PDFs. Although the total content was not as low as that of 1.5% or 2.5% glucose solutions, it was lower than that of 4.25% glucose solutions. Notably, the GDP profile for Extraneal differed from those for glucose-based solutions, presumably because Extraneal contains polyglucose as the osmotic agent and is presented in a single-chamber bag. The osmotic agent is sterilized in the presence of lactate, generating a GDP profile with approximately 50% of the total GDP concentration being attributable to AcA formation. In that respect, the GDP profile for Extraneal is quite similar to that for conventional single-chambered PD solutions, but at a considerably lower level. That finding is consistent with the results of a study by Zimmeck *et al.*, which showed that AcA formation depends on pH and the presence of lactate (21).

The results of the present study confirm those of Erixon *et al.*, who showed that separating glucose from buffer and electrolytes in a double-chambered bag, together with a low pH in the glucose compartment during sterilization and extended storage, are the critical factors that determine GDP formation in PDFs (18). In accord with the data published by Erixon *et al.*, we found that GDP concentrations varied markedly in the PDFs on the market.

Dose-dependent toxicity has been described for all measured GDPs (12,27–29) except for the recently characterized glucosone and 3-DGal (25,30). In our study, 3,4-DGE, which is considered the most toxic of the known GDPs (15–17), showed the highest concentration differences between the investigated low-GDP glucose PDFs. However, the importance of each of the 10 investigated GDPs with respect to adverse clinical outcomes in PD patients is still unclear. Thus, the individual concentration of a GDP might not represent its effect on the overall toxicity attributable to GDPs in PDFs. Conclusions about the importance of individual GDPs for clinical endpoints therefore have to be drawn with caution.

CONCLUSIONS

Delflex Neutral pH is the first FDA-approved biocompatible PDF with neutral pH and low GDP content. The data presented here show that the Delflex Neutral pH system can be easily handled by patients and nurses, and that it consistently delivers a mixed solution with a final pH range of 7.0 ± 0.4 . Only 2 of the 5 other tested solutions were found to deliver similarly low GDP concentrations

at a neutral pH. Detailed comparisons of GDP profiles showed marked variation between the available low-GDP solutions.

DISCLOSURES

All authors are employees of Fresenius Medical Care.

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