COMMENTARY

HYPERBRANCHED POLYGLYCEROL: A FUTURE ALTERNATIVE TO POLYGLUCOSE IN PERITONEAL DIALYSIS FLUIDS?

The ideal peritoneal dialysis fluid (PDF) should have a physiologic electrolyte and buffer composition and be supplemented with an osmotic agent that is non-toxic, nonimmunogenic, and not rapidly absorbed to the plasma compartment, but if so, then rapidly metabolized. Furthermore, it should produce steady osmotic ultrafiltration (UF) over the course of a dwell. So far, glucose (G) has been the universally used osmotic agent in peritoneal dialysis (PD), based on its relative efficiency, low cost, safety, and rapid metabolism in plasma. In addition, commercially available PDFs containing icodextrin (ICO) or amino acids (AAs) have been in clinical use for a long time.

Over the years, improvements in solution composition were initially restricted to changes in buffer and electrolyte composition, particularly focusing on replacing lactate with bicarbonate (1,2). Later, manufacturers took measures to reduce the toxicity of G by minimizing the concentration of glucose degradation products (GDPs) through the production of PDFs in multi-compartment bags (3,4). These more “biocompatible” PDFs, having a neutral pH and being low in GDPs, show lower *in vitro* and *in vivo* toxicity, but tend to produce lower peritoneal UF volumes and higher urine volumes than conventional PDFs (5).

Despite lower toxicity, the long-term beneficial effects of “GDP-free” PDFs have been hard to prove (6–8). However, the recently published *balANZ* study suggests that, compared with conventional PDFs, biocompatible PDFs may delay the onset of anuria and reduce the incidence of peritonitis (9). And yet, the peritoneal absorption of G during PD has both cytotoxic and systemic metabolic effects, which highlights the need to explore osmotic agents other than G for PD.

The clinical availability of ICO has provided improved fluid removal and can be considered to have mitigated the negative impact of the “fast transporter” status on outcomes in PD (10). In malnourished PD patients, AAs

may improve protein-nutrition status whenever protein intake is a cause for the malnutrition (11); however, AAs are not more efficient than G as an osmotic agent (12). Nevertheless, novel fluid exchange strategies that alternate an AA-based solution and an ICO-based solution with two low-GDP G-based solutions during the PD day can reduce the total G load on the peritoneum (13). Also, combination fluids using ICO and G together as osmotic agents have been reported to be beneficial, especially in heavily volume-overloaded patients (14).

Recently, L-carnitine [molecular weight (M_w): 161] was proposed as a novel osmotic agent and tested for a short time in both rodent and human studies (15). The physical properties of L-carnitine are similar to those of G, and the molecule is chemically stable and has been shown to have a good safety profile. However, from an osmotic point of view, L-carnitine is not superior to G. In fact, as a solute, it is slightly smaller than G (Stokes–Einstein radius of approximately 3.4 Å), and it is rapidly diffusible across the peritoneal membrane.

With respect to osmotic efficiency, high M_w agents are preferable to low M_w agents. A high M_w osmotic agent is thus osmotically more efficient per mole of solute because of a higher osmotic reflection coefficient (σ). Furthermore, the absorption of the osmotic agent to plasma by diffusion is less pronounced. However, simultaneously, the molar concentration per unit solute weight (the number of osmotically active molecules per gram of solute) is diminished. Computer simulations using the three-pore model have calculated that the theoretical “trade-off” point between those two features occurs at a rather low solute M_w —on the order of 1–4 kDa (16). Actually, in a commercial ICO solution, polydispersity of the dextrin molecules leads to about 70% of the molecules being smaller than 3 kDa, with only about 25% (3 mmol/L in 12 mmol/L of the osmotic agent) acting as colloids (17). Note, however, that plasma colloids represent only slightly more than about 1 mmol/L of

osmotically active solute in plasma, and yet they produce a colloid osmotic pressure of about 25 mmHg.

In this issue of *Peritoneal Dialysis International*, Mendelson *et al.* (18) introduce a novel osmotic agent, hyperbranched polyglycerol (HPG). As an osmotic agent, HPG fulfills the criteria of being more or less ideal in size and physical properties. In a proof-of-concept study, it was tested in short-term rat experiments. Hyperbranched polyglycerol has a rather low-grade polydispersity, with a polydispersity index (M_w/M_n) of 1.1 and a weight-average M_w of about 3 kDa. The calculated Stokes–Einstein radius is 10.6 Å, which is approximately triple that of G (Table 1). Because of the larger Stokes–Einstein radius, the calculated σ is, according to the three-pore model, approximately four times that of G (0.22 vs 0.05), and the peritoneal mass transfer area coefficient is approximately one sixth that of G (1.3 mL/min vs 8 mL/min in humans, Table 1). On the other hand, the number of osmotically active particles per gram of solute is just one sixteenth that for G! Therefore, as a percentage, the “equi-osmotic” efficiency concentration of HPG (0.33 mmol/g, and $\sigma = 0.22$) compared with 1.36% G (5.6 mmol/g, and $\sigma = 0.05$) would be approximately 5% (Table 1). The concentration of HPG that is osmotically equivalent to 2.27% G can be calculated to be approximately 8% (Table 1), which is more or less exactly what was found when 30 mL of a 7.5% HPG solution was assessed with respect to UF properties during a 4-hour dwell in a rodent model of PD (18). Actually, an 8% HPG solution should be slightly

more efficient than 2.27% G in producing UF because, compared with G, HPG has lower diffusivity and less reabsorption to the plasma compartment. Because of higher net UF during a 4-hour dwell, the total small-solute (cf. urea) removal should be superior with HPG than with an equi-osmotic G solution, as was actually found in the foregoing dwell study.

Overall, HPG seems to be nontoxic, nonimmunogenic, and highly biocompatible. In acute dwell studies, HPG was not only superior to intermediate-strength G-based PDF with respect to UF and urea clearance, but it also seemed to result in less neutrophil infiltration and reduced thickness of the submesothelial compact zone. Thus, while exposure to G-based PDF induces cytoplasmic vacuolization and caspase 3-independent necrotic cell death, the same was not seen with PDF containing HPG. However, those observations came from just a single dwell, and so subsequent studies will have to focus on the long-term safety and biocompatibility of HPG solution.

Despite its high M_w , HPG will be avidly absorbed to the plasma from the peritoneal fluid, and so the issue of HPG metabolism in plasma arises. Will HPG accumulate in plasma during long-term use? Other questions relating to the stability of HPG and its degree of polydispersity also arise. Are the HPG molecules metabolized in plasma and intraperitoneally?

The theoretical osmolality of a 7.5% monodispersed HPG (3 kDa) solution would be approximately 295 mOsmol/L (75/3 mmol/L + 270 mmol/L), which is actually approximately 25 – 30 mOsmol/L less than was determined experimentally. For a 15% solution, the theoretical osmolality would be approximately 320 mOsmol/L (150/3 mmol/L + 270 mmol/L), which is approximately 100 mOsmol/L less than was measured. Those results indicate that, per liter, the HPG molecules number about twice what was calculated from the HPG concentration (in percentage terms) and the M_w . Thus, the polydispersity of HPG seems to be larger than was specified by the manufacturer.

Finally, although HPG (3 kDa) is rapidly excreted from the circulation and does not accumulate in vital organs in animals with normal renal function, what are the kinetics in nephrectomized animals (those with a glomerular filtration rate of 0)? Actually, it seems that HPG molecules of high M_w (higher than 3 kDa) tend to accumulate in the reticuloendothelial system over time (19). Perhaps HPG solutions should be used for only a single daily dwell. In that respect, it may in future compete with ICO as a PDF used for long dwells.

In summary, the study by Mendelson *et al.* (18) introduces an interesting novel osmotic agent with very

TABLE 1
Calculated properties of glucose and hyperbranched polyglycerol (HPG)

Property	Glucose (0.18 kDa)	HPG (3 kDa)
Stokes–Einstein radius (Å) ^a	3.66	10.6
Reflection coefficient (σ_{TPM})	0.048	0.22
MTAC or PS ^b (mL/min)	7.98	1.13
Concentration (%)		
Equimolar (mmol/L)	1.36 (75)	22.5 (75)
Equi-osmotic efficiency ^c	2.27 (126)	37.8 (126)
	1.36	4.9
	2.27	8.2

TPM = three-pore model; MTAC = mass transfer-area coefficient; PS = permeability surface area.

^a Solute radius (a_e) calculated from $a_e = 0.486 \times [\text{molecular weight } (M_w)]^{0.385}$.

^b $A_0/\Delta X = 21\,000$ cm in humans.

^c Calculated from the molar concentration times the solute reflection coefficient (σ).

promising properties for UF (osmotic) behavior and short-term biocompatibility. On a molar basis, it appears to be more efficient than G by a factor of 4 in producing osmosis (UF) across the peritoneum. However, data on the metabolism of HPG in plasma and on its potential for plasma accumulation during long-term use are essentially lacking. Whether HPG breaks down intraperitoneally is also not well studied. Finally, the long-term biocompatibility of HPG is unknown. Although many issues remain to be addressed, the introduction of HPG represents an important step forward on the path toward improved osmotic agents in fluids for PD.

DISCLOSURES

BR has received speaker's honoraria from Fresenius Medical Care and is participating in a clinical trial with Fresenius Medical Care.

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