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Future of icodextrin as an osmotic agent in peritoneal dialysis

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One of the most notable advances in peritoneal dialysis (PD) technology during the past two decades has been the development and introduction in clinical practice of a new generation of PD solutions designed to address specific clinical and biologic aspects of the therapy. These solutions have been developed to tackle the issues of enhanced ultrafiltration (alternative osmotic agents), nutritional support (amino acid containing solutions), and peritoneal membrane preservation (alternate buffer systems and physiologic pH) [1–3]. Icodextrin-based solutions have been the longest in clinical use since their development two decades ago [4], and have accumulated large clinical experience regarding their efficacy and safety. This is reflected in their widespread acceptance and common use in countries where they are available. Icodextrin-based solutions differ from the conventional PD fluids not only in the nature of the osmotic agent, but also in the mechanism by which they lead to ultrafiltration. These solutions induce effective transcapillary ultrafiltration through colloid osmosis during dwells of more than 12 hours. Therefore, icodextrin-based solutions promote an equal or better and more long-lasting ultrafiltration profile than glucose solutions during the long dwell without the problems of hyperosmolality and high glucose content of the latter.

In parallel with the advances in PD solutions, there is growing evidence of the common presence of over-hydration in dialysis patients, particularly in anuric long-term PD patients, in addition to the cumulative appreciation of the risk for cardiovascular mortality that chronic fluid overload represents [5]. The progressive loss of residual renal function leads to greater reliance on peritoneal ultrafiltration for the maintenance of fluid balance [6]. If this is not pursued zealously, a state of chronic over-hydration develops with the predictable nefarious consequences. When enhanced peritoneal ultrafiltration is attempted with traditional hypertonic glucose-based solutions, the greater glucose exposure may lead to higher peritoneal permeability and consequent greater difficulty in peritoneal fluid removal. Thus, there seems to be a vicious circle in long-term PD treatment, in which the loss of renal function and development of hyper-permeable membrane require the use of more hypertonic solutions, which in turn may exacerbate membrane hyperpermeability and can perpetuate a state of over-hydration and loss of ultrafiltration. The use of an alternative high molecular weight osmotic agent for the long dwell can be an interesting alternative in preventing this situation, and therefore may have a positive impact on reducing the unacceptably high cardiovascular mortality of PD patients. This is the most important systemic effect of the icodextrin-based solutions. As discussed in this review, various other positive systemic and local effects may contribute to make this solution the standard prescription for the long dwell in PD patients in the future.

Key words: dialysate solution, ultrafiltration, nutritional support, membrane preservation, renal replacement therapy, CAPD, APD.

THE PROBLEM OF FLUID OVERLOAD IN PERITONEAL DIALYSIS

It is now widely accepted that in order to achieve good clinical outcomes with dialysis treatment, one should provide adequate solute and fluid removal. Strategies to enhance fluid removal in dialysis patients are summarized in Table 1. Solute removal has been addressed in a large number of clinical studies, most recently in the ADEMEX study [7]. However, until recently fluid removal has been largely neglected in most of the studies and guidelines published [6]. However, it is clear that fluid status has gained increased interest in the PD scientific community in recent years [8]. In parallel, despite the advantageous effect of PD on hemodynamic stability [9], cardiovascular disease remains the most common cause of morbidity and mortality in this population [10, 11]. Volume overload leads to the development of hypertension and left ventricular hypertrophy, which are directly associated with increased risk of sudden death, stroke, and congestive heart failure [12]. Indeed, clinical features of over-hydration are observed in roughly one fourth of the patients on continuous ambulatory peritoneal dialysis (CAPD) [13]. In a recent study, the extracel-

Table 1. Strategies to enhance fluid removal in dialysis patients

1. Reduce salt (and fluid) intake
2. Preserve GFR and use diuretics
3. Prescribe longer HD sessions
4. Consider daily HD
5. Short HD is effective but may be associated with problems related to cardiovascular instability and sodium balance
6. Continuous dialysis (that is, PD) is advantageous as it allows continuous fluid removal
   a. Glucose-based solutions are efficient for short dwells, but are less effective in long dwells, particularly in high PSTR patients, and during peritonitis
   b. Icodextrin-based solution provides sustained ultrafiltration during long dwells, especially in high PSTR patients, and during peritonitis

Abbreviations are: GFR, glomerular filtration rate; HD, hemodialysis; PD, peritoneal dialysis; PSTR, peritoneal small solutes transport rate.

lular volume in CAPD patients was similar to that of hemodialysis patients before the dialysis session, indicating that the CAPD patients were fluid overloaded despite their seemingly stable clinical status [abstract; Wu et al, *Perit Dial Int* 21(Suppl):S8, 2002]. Similarly, Koonings et al showed that PD patients were over-hydrated when compared to transplanted patients (abstract; Koonings et al, *Perit Dial Int* 22:142, 2002).

This state of over-hydration may not be only a sign of clinical neglect, but may be influenced by developments during the course of PD treatment. First, during long-term PD treatment, the peritoneal membrane undergoes functional as well as structural alterations that may be the consequence of many factors such as peritonitis and continuous exposure to dialysis solutions with high concentrations of glucose and glucose degradation products, low pH, and high osmolality. The most common functional alteration during long-term CAPD is increased peritoneal small solutes transport rate (PSTR) [14], resulting in impaired ultrafiltration and decreased dialysis efficiency [15]. Fluid volume control becomes more demanding when anuria develops following the natural progression of the underlying renal disease. Depending on the level of renal function at initiation of dialysis, anuria will become evident in most patients within three years after the initiation of PD. In parallel, peritoneal ultrafiltration may decline in a subset of patients, primarily because of high PSTR, and clinical manifestations of impaired ultrafiltration appear in as many as 30% of CAPD patients after six years on PD [16]. It is conceivable that taken together these two factors, the increased PSTR with loss of ultrafiltration and declining residual renal function (RRF), lead to a state of chronic fluid overload in PD patients, unless adequate treatment is initiated. RRF has a significant role in the maintenance of adequate volume control in PD patients. It has been reported that approximately 80% of the patients with end-stage renal disease (ESRD) are hypertensive when they start dialysis [12]. The prevalence decreases to 40% in CAPD patients at the end of 1 year on dialysis [17]. However, after the first years on dialysis, blood pressure control becomes more difficult, requiring a greater number of antihypertensive medications [18]. Lameire et al also found that although the prevalence of left ventricular hypertrophy (LVH) and hypertension decreased significantly in the first three years, both these risk factors go back to similar levels after five years, as at the start of CAPD treatment [11, 17, 19].

The results of the recently published ADEMEX study [7] as well as some previous reports [20, 21] suggest that parameters other than small solute removal (Kt/V urea or creatinine clearance) are more important in determining clinical outcome in PD patients. The results of the ground-breaking ADEMEX study question some of the concepts defined by previous studies and current guidelines. As an example, the CANUSA study considered renal and peritoneal clearances equivalent in influencing survival, and interpreted their findings of a correlation between total projected clearance and survival as proof of a significant impact of small molecule clearances on clinical outcome [22]. However, a more detailed examination of the data showed that there was no effect of peritoneal clearance on outcome [23].

One important reason why residual renal clearance (rather than peritoneal clearance) is a predictor of patients' clinical outcome is that the contributions of fluid removal in peritoneal clearance and renal clearance are different. A higher renal Kt/V, in general, represents increased fluid removal. On the other hand, higher peritoneal Kt/V does not necessarily mean increased fluid removal [15]. Peritoneal fluid removal, or in other terms, net ultrafiltration, may be negative, particularly during the long dwell cycle and with the use of a low glucose concentration solution [24]. By increasing the dialysis dose, one can achieve higher small solute clearances even without net fluid removal during PD [15]. Therefore, higher small solute clearances achieved by increasing the dialysis dose may not necessarily be associated with better clinical outcome, unless adequate net fluid removal is achieved. It is thus not surprising that the residual renal function and peritoneal dialysis transport characteristics may have different effects on patients' outcome [20, 25, 26]. By the same rationale, although incremental peritoneal clearance in general is not considered a strong determinant of clinical outcome, the peritoneal transport status has in some studies of CAPD patients been found to affect outcome: increased PSTR was associated with increased mortality and decreased technique survival, although it is easier to achieve creatinine clearance (C_{Cr}) targets for high PSTR patients [15, 27, 28]. These associations may reflect the difficulties inherent in fluid removal in these patients with CAPD and traditional glucose-based solutions. More recent studies with APD and ico-

dextrin use (and expected better fluid control) have not found this association, suggesting that volume removal rather than the peritoneal transport function is the determining factor (Brown et al, unpublished observation).

These findings suggest that the fluid overload caused by insufficient ultrafiltration may contribute to the increased mortality in anuric PD patients. It is therefore possible that improved fluid balance in these patients, especially in high transporters, will improve their clinical outcome. Undoubtedly, this will be an important area for studies during the coming years.

VIRTUAL NON-GLUCOSE OSMOTIC AGENTS IN PERITONEAL DIALYSIS

A peritoneal dialysis solution containing glucose polymers as osmotic agent differs from the glucose-based solution, since it induces *trans*capillary ultrafiltration without being hypertonic. The icodextrin-based solution is currently the only safe and efficient non-glucose large molecular weight osmotic agent for the long dwell and it is now available in several countries for clinical use (Extraneal®; Baxter Healthcare, McGaw Park, IL, USA). The icodextrin-based solution is a polymer of glucose produced by the hydrolysis of cornstarch and it contains a spectrum of polymer molecules with an average molecular weight of 16.2 kD [29]. The polymers consist of glucose units linked predominantly by α-1-4 glucosidic bonds, with a small proportion of branches linked by α-1-6 glucosidic bonds. After absorption, the polymers are degraded to disaccharides, maltose, and eventually glucose [30]. Icodextrin is iso-osmolar (285 mOsm/kg) to the plasma, and its pH is 5.2 to 5.6. From a metabolic point of view, icodextrin can be considered as a virtual non-glucose osmotic agent because of the slow release of glucose molecules from icodextrin (a description of the metabolic effects of icodextrin can be found elsewhere in this Supplement issue).

The ultrafiltration yielded by a 7.5% icodextrin-based dialysis solution is higher than the ultrafiltration generated by 1.36% glucose (1.5% dextrose) solutions during a six-hour dwell, despite its lower osmolality (285 vs. 347 mOsm/kg). This demonstrates the colloid osmotic (instead of crystalloid osmotic) mechanism of action of icodextrin. Moreover, when used for the 8 to 12 hour long-dwell in CAPD and APD patients, icodextrin 7.5% provides equivalent or higher ultrafiltration than that provided by 3.86% (486 mOsm/kg) glucose (4.25% dextrose) solution [29, 31, 32].

EFFECT OF ICODEXTRIN ON PERITONEAL TRANSPORT

There are several barriers to solutes and water transport from peritoneal capillaries into the peritoneal cavity: fluid films within peritoneal capillaries, the capillary endothelium, the capillary basement membrane, the interstitium, the mesothelium, and stagnant fluid films within the peritoneal cavity (Fig. 1) [33]. The capillary endothelium constitutes a very selective barrier for solute diffusion and is probably the most important resistance during PD [33, 34]. The transport of fluid and solutes across the capillary endothelium is generally considered to occur through a system of three pores [24]: the large pores (radii that exceed 150 Å) that allows the transport of macromolecules such as serum proteins, corresponding to less than 0.1% of the total number of pores; the small pores (radii of 40 to 50 Å) that are involved in the transport of low molecular weight molecules such as glucose, urea, creatinine and β2-microglobulin, corresponding to 50 to 60% of the total number of pores; and finally the ultra-small, "*trans*cellular" aquaporin pores (radii smaller than 3 Å) that are involved only in water, but not solute transport.

Icodextrin and peritoneal fluid transport

Macromolecules such as glucose polymers can induce *trans*capillary ultrafiltration even under isotonic conditions. The process of colloid osmosis is based on the principle that water is transported from the capillaries in the direction of relative excess of impermeable large solutes, rather than down an osmotic gradient (as in the case of glucose-based solutions). This process implies that icodextrin removes fluid from the body by inducing water transport through small pores. Since the icodextrin solution is not hypertonic in relation to the plasma, no transport through the ultra-small pores is induced. Based on the reflection coefficients of urea, creatinine, urate and glucose, the average reflection coefficient for icodextrin was estimated as 0.76, implying that the maximal pressure gradient across the peritoneal membrane was 37 mm Hg, in contrast to the 88 mm Hg exerted by 3.86% glucose solution [35]. Because of its low absorption from the dialysate, icodextrin maintains this gradient for several hours, and after a seven-hour dwell, a 36 mm Hg pressure difference is still present, whereas this pressure difference approaches zero when glucose-based solutions are used. As a result, sustained ultrafiltration is obtained with icodextrin even during very long dwells. Furthermore, it is possible that icodextrin results in decreased fluid reabsorption from the dialysate [36], further contributing to improved net ultrafiltration.

Icodextrin and peritoneal sodium transport

During peritoneal dialysis, sodium is transported by diffusion (dependent upon the gradient between plasma and dialysate), by convection due to ultrafiltration, and by convection due to peritoneal fluid absorption (lymphatic and interstitial absorption). The sodium transport is dependent upon the concentration of glucose solution

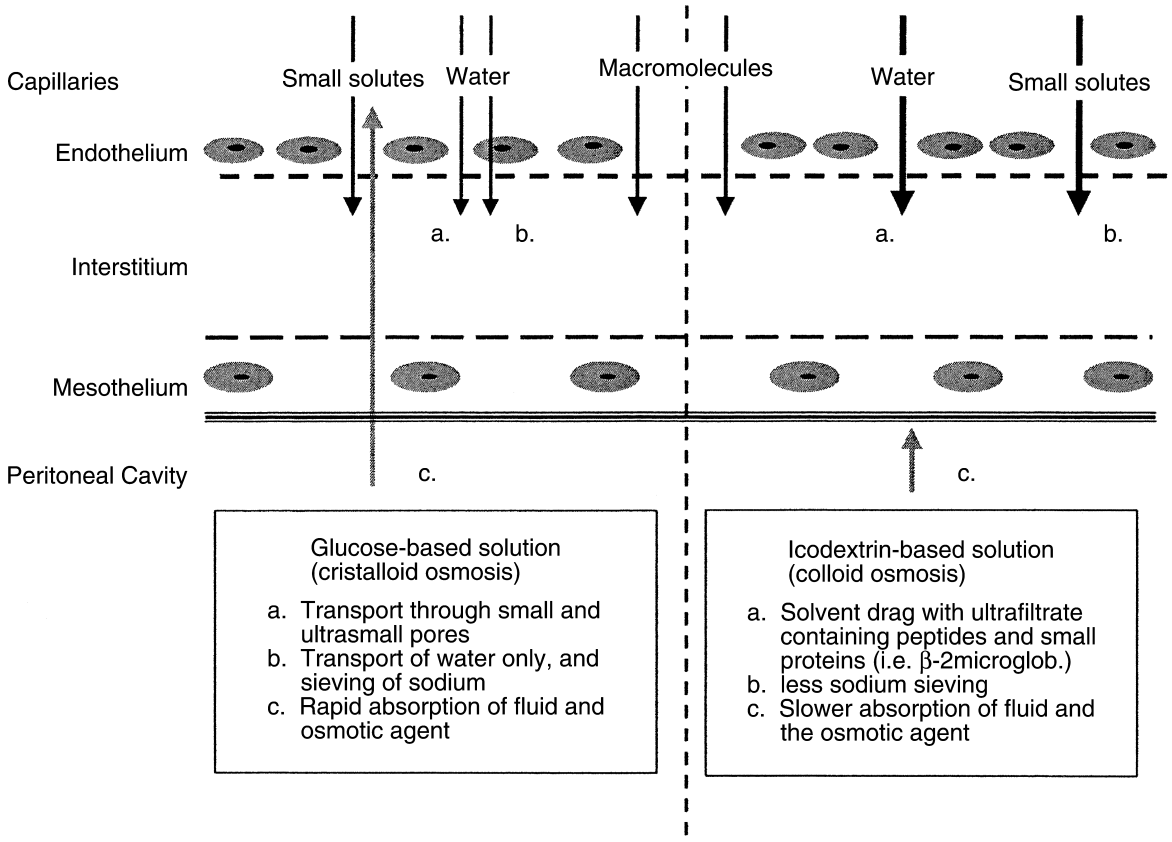

Fig. 1. Proposed pathways for the peritoneal transport of fluid and solutes based on the three pore model and experimental and clinical data. The prevailing transport routes when glucose-based solution (including the glucose absorption that occurs in long dwells) is used (left) and when icodextrin-based solutions is used (right).

used and transport characteristics of the membrane, and net sodium removal is highly correlated to the net ultrafiltration [37]. A detailed evaluation of sodium transport (taking into account peritoneal absorption) with icodextrin solutions has not yet been performed, but one can assume that due to characteristics of the icodextrin solutions, beneficial effects on sodium removal during the long-dwell can be extrapolated due to the prolonged ultrafiltration profile in combination with less sieving of sodium. Indeed, Plum et al recently showed that the total dialysate sodium removal increases when icodextrin is used as an osmotic agent [38]. Moreover, because there is an absence of sodium sieving during the icodextrin dwell, the amount of sodium per volume of ultrafiltrate is expected to be higher than sodium removed with osmotic agents associated with high sodium sieving (that is, glucose solutions).

Icodextrin and peritoneal small solutes transport

Pannekeet et al have shown similar mass transfer area coefficients of urea, creatinine and urate, comparing 3.86% glucose (4.25% dextrose) and 7.5% icodextrin solutions in a four-hour dwell [39]. This implies that the most important determinant of small solute transport (the peritoneal membrane surface area available for diffusive transport) was not influenced by the tonicity or type of solution evaluated. Thus, the increased dialysate volume results in increased removal of small solutes. This has been documented clinically in studies of icodextrin, in which the higher ultrafiltration response with icodextrin in comparison to 2.5% dextrose solutions was also manifested in higher solute clearance [38].

Icodextrin and peritoneal transport of proteins

In single dwell studies comparing icodextrin to glucose solutions, β2-microglobulin removal was significantly higher with the use of icodextrin [32, 35]. These findings of higher clearance of small proteins with the use of icodextrin support the hypothesis that icodextrin acts through the small pores, and also that icodextrin increases the "solvent drag." This phenomenon most likely is caused by increased convective transport of solutes including peptides and small proteins through the small pores. The radius of β2-microglobulin (16 Å) allows its passage through the small pore system. In contrast, when clearances of albumin (36 Å) and α2-macroglobulin were ana-

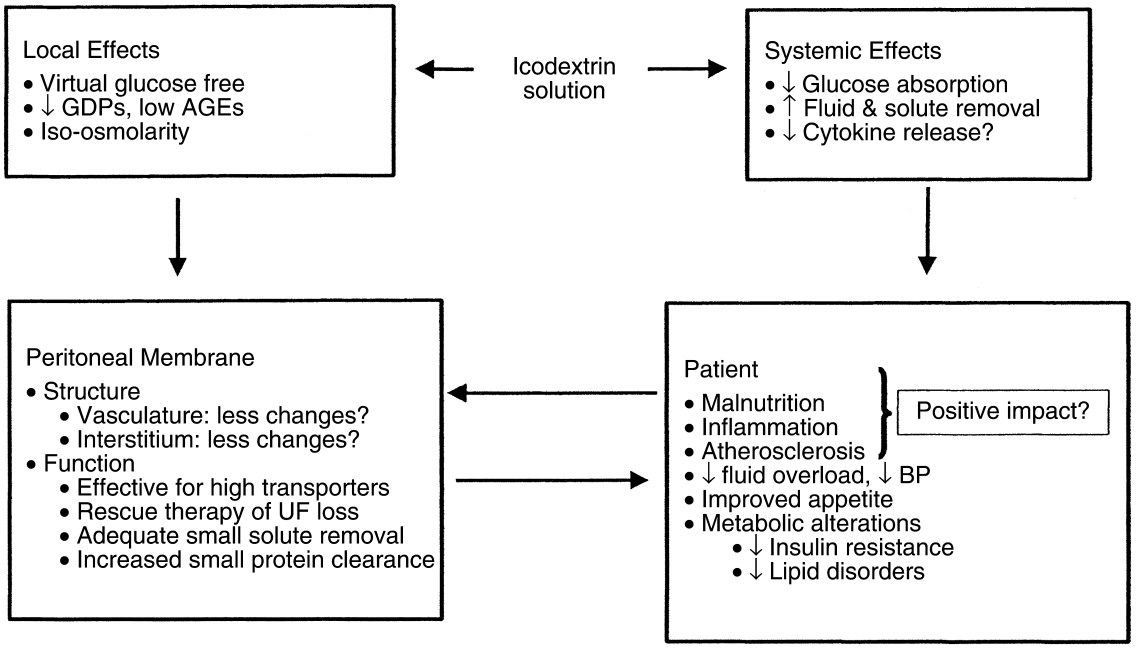

Fig. 2. Possible local (peritoneal membrane) and systemic effects of icodextrin solutions. Question marks denote possible but not yet documented effects, which should be subject of future studies.

lyzed, no differences between icodextrin and hypertonic glucose solutions were found [39]. The same findings were present when Krediet et al analyzed clinically stable patients before and four weeks after the initiation of icodextrin use for the overnight dwell. A 28% increase in the β2-microglobulin transport was observed, due to an increase in convective transport [40]. This mechanism of action on small protein removal can result in further potential benefits of icodextrin solutions. In this line of rationale, Opatrna et al showed higher leptin removal with the use of icodextrin, compared to glucose solutions (abstract; *Perit Dial Int* 22:116, 2002). Acute studies on appetite in an experimental rat model indicate that icodextrin-based dialysis solutions may result in less inhibition of appetite than glucose based solutions; this effect is most likely due to the avoidance of rapid glucose absorption [41]. With the potential adverse effects of leptin on appetite, and atherosclerosis in mind, further studies are needed to analyze the consequences of higher removal of leptin in PD patients treated with icodextrin. The same concept could be applied to the effects of icodextrin removal of other small proteins of the same molecular weight. This is yet another area for future studies. The prospect of improving the clearance of middle molecules is very promising.

LOCAL (INTRAPERITONEAL) EFFECTS OF ICODEXTRIN SOLUTIONS

The isoosmolar icodextrin solution may be potentially less damaging to the peritoneum and to peritoneal defense compared to hyperosmolar glucose solutions [42, 43]. Several ex vivo studies have demonstrated improvements in both peritoneal and mesothelial cell function in patients using icodextrin-based dialysis solution, while using conventional solutions for all other exchanges [44, 45]. Icodextrin has been demonstrated to exert no long-term toxicity, and some studies suggested that it is more biocompatible to the peritoneum than glucose, particularly due to its isoosmolarity [42]. In addition, the concentration of glucose degradation products of the icodextrin-based dialysis solution is very low compared to that of glucose-containing solutions, yielding a significant reduction in in vitro cell cytotoxicity, glycation of proteins, Amadori adduct formation, and advanced glycation end product (AGE) formation [46]. In fact, Ho-dac-Pannekeet et al presented information indicating that treatment with icodextrin-based solutions results in decreased glycosylated proteins in the peritoneal membrane [47]. The icodextrin-based solutions therefore potentially may contribute to preserve the structural and functional properties of the peritoneal membrane (Fig. 2).

SYSTEMIC EFFECTS OF ICODEXTRIN SOLUTIONS

In addition to these local effects, the icodextrin solution also may have various positive systemic effects (Fig. 2). The most well-documented systemic effects are related to improved fluid removal in patients with increased peritoneal surface area as demonstrated in com-

Table 2. Advantages of icodextrin-based solutions over 4.25% dextrose solutions in peritoneal dialysis

Functional advantages
• Long-lasting ultrafiltration
• Superior ultrafiltration in high and high average transporters
• Higher clearance of middle molecules (β2-microglobulin)
• Greater sodium removal per ultrafiltrate volume
Metabolic advantages
• Absence of hyperglycemia and hyperinsulinemia
• Lower caloric load
• No rapid abdominal distension and less acute discomfort
• Lower glucose degradation products
• No hyperosmolar damage to peritoneal membrane
• No peritoneal glucose exposure

puter simulations [48] and in clinical studies [32]. Icodextrin has been used successfully during peritonitis [49, 50], and can prevent the temporary decline of ultrafiltration due to the increased absorption of glucose induced by the inflammation and vasodilation in the peritoneal membrane, when using glucose based solutions [39, 51]. Indeed, the ultrafiltration profile was considerably better in patients with signs of intraperitoneal inflammation, as estimated by the intraperitoneal levels of interleukin-6 [abstract; Pecoits-Filho et al, *Perit Dial Int* 22(Suppl 1):S13, 2002]. Furthermore, icodextrin may be of particular value in high transporters [32, 52]. Improved fluid removal may have various positive effects. For example, in a crossover study, Woodrow et al reported reduction of the anti-hypertensive medication in 6 out of 14 APD patients using icodextrin. Furthermore, blood pressure was significantly reduced, and this effect correlated with changes in body weight and body water compartments estimated by multifrequency bioelectrical impedance. These authors concluded that the use of icodextrin for the daytime dwell in APD results in improved fluid and blood pressure control [53]. Additionally, in terms of the systemic metabolic benefits, an analysis by the MIDAS study group has shown a significant reduction in total cholesterol and low-density lipoprotein (LDL) cholesterol, especially in patients with baseline hypercholesterolemia [54]. Finally, better fluid control may not only facilitate blood pressure and metabolic control, and therefore prevention of cardiovascular disease, but also may reduce the risk for inflammation and malnutrition, which are strongly associated with cardiovascular disease [1, 5]. In a recent study, Niebauer found that chronic congestive heart failure was associated with elevated levels of plasma pro-inflammatory cytokines and that diuretic treatment controlling volume status in these patients was associated with a significant decrease in systemic endotoxin levels [55]. The possible positive systemic effects of icodextrin on the malnutrition, inflammation and atherosclerosis (MIA) syndrome [56, 57] require further investigation.

FUTURE CLINICAL USE OF ICODEXTRIN SOLUTIONS

There is now an extensive clinical experience with the icodextrin-based solution, and its efficacy and safety are well documented. Long-term clinical experience now extends over many years in an increasing number of patients [31, 38, 50, 52, 58], and it has been demonstrated that this solution may extend CAPD technique survival in patients with UF failure [51]. Therefore, it is likely that this solution will become the standard solution for the long dwell in PD. Further developments, such as the combination of a lower concentration of icodextrin with glucose [abstract; Jenkins et al, *Perit Dial Int* 22(Suppl 1):S118, 2002] and perhaps other osmotic agents such as amino acids [2] and glycerol [59] possibly could extend its future use to also encompass shorter exchanges.

SUMMARY

In summary, the use of icodextrin as an osmotic agent increases ultrafiltration during the long dwell in PD patients, particularly during peritonitis and in high transporters. Thus, the effect of icodextrin is most powerful precisely in those patients who need it most, namely the high transporters. A major advantage is that icodextrin provides increased ultrafiltration and clearances during long dwells, while avoiding problems with excessive glucose absorption. Various unwanted systemic and local effects of the standard glucose-based dialysis solutions can be avoided with the use of icodextrin (Table 2), and this may potentially improve both technique survival and patient survival especially in PD patients with inadequate UF. Therefore, it is likely that the icodextrin-based solution will be the standard solution for the long dwell in the majority of PD patients in the future.

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