

## Review Article

# Recommendations for the use of icodextrin in peritoneal dialysis patients

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**SUMMARY:** Icodextrin is a starch-derived, high molecular weight glucose polymer, which has been shown to promote sustained ultrafiltration equivalent to that achieved with hypertonic (3.86%/4.25%) glucose exchanges during prolonged intraperitoneal dwells (up to 16 h). Patients with impaired ultrafiltration, particularly in the settings of acute peritonitis, high transporter status and diabetes mellitus, appear to derive the greatest benefit from icodextrin with respect to augmentation of dialytic fluid removal, amelioration of symptomatic fluid retention and possible prolongation of technique survival. Glycaemic control is also improved by substituting icodextrin for hypertonic glucose exchanges in diabetic patients. Preliminary *in vitro* and *ex vivo* studies suggest that icodextrin demonstrates greater peritoneal membrane biocompatibility than glucose-based dialysates, but these findings need to be confirmed by long-term clinical studies. This paper reviews the available clinical evidence pertaining to the safety and efficacy of icodextrin and makes recommendations for its use in peritoneal dialysis.

**KEY WORDS:** blood glucose analysis, CAPD, dialysis solutions, drug eruptions, glucans, isotonic solutions, kidney failure, practice guidelines, ultrafiltration.

## INTRODUCTION

Icodextrin is a starch-derived, high molecular weight glucose polymer that was first used as an osmotic alternative to glucose in peritoneal dialysis in the 1980s.<sup>1–4</sup> Since that time, there has been increasing interest in the use of icodextrin-containing peritoneal dialysis (PD) solutions because of their demonstrated ability to induce sustained peritoneal ultrafiltration. Fluid removal is achieved by colloidal, rather than crystalline, osmotic pressure and is most pronounced over prolonged dwells (12–16 h).<sup>5–8</sup> There is also emerging evidence that this isosmotic solution may be less damaging to the peritoneal membrane than glucose-based dialysates.<sup>9–11</sup> A 7.5% icodextrin-based solution (Extraneal, Baxter Healthcare, Castlebar, Ireland) is currently approved for marketing in 31 coun-

tries, and is used by over 8000 PD patients worldwide. In Europe, where the product has been available for more than 9 years, nearly one-third of the entire PD population (or approximately 7000 patients) currently use icodextrin.

Recently, the International Society of Peritoneal Dialysis (ISPD) Ad Hoc Committee on Ultrafiltration Management in Peritoneal Dialysis recommended that icodextrin be used for the long dwell in high transporter patients with a net peritoneal ultrafiltration of less than 400 mL/4 h.<sup>12</sup> However, in spite of emerging evidence for a more expanded role for icodextrin in PD, there have been no other published guidelines on this subject. The aim of this paper was to establish indications for icodextrin in PD and to review the available evidence supporting these recommendations.

## EVIDENCE SUMMARY

1. Icodextrin can be safely and effectively substituted for glucose-based dialysates in one long-dwell peritoneal

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- dialysis exchange per day (such as overnight exchanges in continuous ambulatory peritoneal dialysis (CAPD) or daytime exchanges in continuous cyclic peritoneal dialysis (CCPD)) (NHMRC evidence level II – two well-run randomized controlled trials).
2. Icodextrin promotes sustained ultrafiltration and small solute clearances equivalent to that achieved with hypertonic (3.86%/4.25%) glucose exchanges (NHMRC evidence level II – two well-run randomized controlled trials) and is an effective treatment for patients with impaired dialytic fluid removal, particularly high and high-average transporters (NHMRC evidence level III-2 – small cohort studies), and those with acute peritonitis (NHMRC evidence level II – small randomized controlled trials).
  3. Prescription of icodextrin to patients with impaired peritoneal ultrafiltration may prolong PD technique survival (NHMRC evidence level IV – small case series).
  4. Substitution of icodextrin for one daily long-dwell glucose exchange reduces systemic carbohydrate absorption (NHMRC evidence level II – reasonable quality randomized controlled trial), and may be a useful strategy for improving glycaemic control in diabetic PD patients, particularly those requiring hypertonic glucose exchanges to maintain ultrafiltration (NHMRC evidence level IV – small case series).
  5. The ability of icodextrin to promote sustained ultrafiltration during long-dwell exchanges, avoid peritoneal membrane exposure to glucose, and reduce systemic carbohydrate absorption, make it potentially highly suitable for incremental PD regimens, although its utility for this indication has not yet been subjected to rigorous study (NHMRC evidence level IV – small case series).
  6. Icodextrin demonstrates greater biocompatibility than glucose-based dialysates in *in vitro* and *ex vivo* studies, but there are as yet no long-term clinical studies comparing the relative effects of icodextrin versus glucose on peritoneal membrane structure and function.

#### ROLE OF ICODEXTRIN IN PERITONEAL ULTRAFILTRATION MANAGEMENT

To date, there have been two open-label, randomized controlled trials of glucose polymer, which have both demonstrated that icodextrin is comparable to hypertonic (3.86%) glucose in terms of net peritoneal ultrafiltration and small solute clearance during long dwells (8–16 h).<sup>13,14</sup> The first of these investigations was the Multicentre Investigation of Icodextrin in Ambulatory Peritoneal Dialysis Study (MIDAS).<sup>13</sup> In this multicentre trial, 209 stable patients from 11 centres (representing approximately 5% of the United Kingdom CAPD population) were randomly allocated to receive an overnight exchange with either 7.5% icodextrin ( $n=106$ ) or con-

ventional (1.36 or 3.86%) glucose solutions. One hundred and thirty-eight patients completed the 6-month study (67 icodextrin, 71 control). An intention-to-treat analysis demonstrated that the mean overnight peritoneal ultrafiltration achieved with icodextrin was equivalent to that of 3.86% glucose at 8 h ( $510 \pm 48$  vs  $448 \pm 60$  mL,  $P=0.44$ ). Following a 12-h dwell, icodextrin tended to promote a greater degree of fluid removal ( $552 \pm 44$  vs  $414 \pm 78$  mL), but the difference just failed to achieve statistical significance ( $P=0.06$ ). There were no observed adverse clinical effects over the period of the study.

A second, smaller, single-centre, randomized controlled trial in CCPD patients compared the ultrafiltration potential of icodextrin ( $n=19$ ) with that of variable glucose strengths ( $n=19$ ) during the daytime dwell (14–15 h).<sup>14</sup> The mean glucose concentration used for daily exchanges in the control group ranged between 2.25 and 2.41%. Twenty-three patients completed 9 months of follow up, and only 13 patients finished the planned 2-year treatment period. Although this generated the potential for survivor bias, daytime and 24-h ultrafiltration volumes were significantly higher in icodextrin- compared with glucose-treated patients at both 3 months (mean differences 126 and 195 mL, respectively;  $P<0.05$ ) and 6 months (182 and 207 mL, respectively;  $P<0.05$ ). Ultrafiltration at subsequent time points was well maintained in the icodextrin group up to 24 months, but was not significantly different from the glucose group. However, overall sample sizes were too small to confidently exclude a type II statistical error. A subsequent, short-duration, random-order, sequential study of 2.27% glucose, 3.86% glucose and 7.5% icodextrin during the long daytime dwell (13.8–15.5 h) in 17 CCPD patients confirmed that median ultrafiltration volumes were comparable between icodextrin and 3.86% glucose (260 vs 100 mL,  $P=\text{not significant}$ ), but were significantly greater than 2.27% glucose ( $-190$  mL,  $P<0.005$ ).<sup>15</sup> Twenty-four hour creatinine clearances were highest in the group receiving icodextrin, possibly secondary to increased ultrafiltration. Importantly, the difference in daytime ultrafiltration between icodextrin and 3.86% glucose was positively correlated with the dialysate: plasma creatinine ratio, suggesting that icodextrin may achieve superior fluid removal compared with glucose-based dialysates in subjects with higher peritoneal membrane transport characteristics. This finding was supported by a small transport study<sup>16</sup> in which a group of 10 stable CAPD patients receiving icodextrin exhibited a strongly positive linear relationship between the icodextrin-induced transcapillary ultrafiltration rate and mass transfer coefficient (MTAC) creatinine. In contrast, when these patients were treated with 3.86% glucose dialysate, an inverse relationship was observed.

Several randomized controlled trials have also demonstrated that icodextrin offers an ultrafiltration advantage compared with glucose-based dialysates in patients with

enhanced membrane permeability caused by acute peritonitis. In the MIDAS study,<sup>17</sup> nine patients in the glucose group and 14 patients in the icodextrin group experienced CAPD-associated peritonitis. During these infective episodes, the mean overnight ultrafiltration volumes decreased slightly from  $218 \pm 354$  to  $185 \pm 218$  mL in the glucose group ( $P = \text{not significant}$ ), but significantly increased in the icodextrin group from  $570 \pm 146$  to  $723 \pm 218$  mL ( $P < 0.01$ ). Similar findings have also been reported by Dratwa *et al.*<sup>18</sup> A randomized study in CCPD patients<sup>19</sup> observed that mean daytime and total 24-h ultrafiltration significantly fell during peritonitis episodes by approximately 600 mL, but were well maintained in icodextrin-treated patients. The mean differences in daytime and 24-h fluid removal between the two groups exceeded 1000 mL.

Although augmented peritoneal fluid removal by icodextrin should intuitively help to correct fluid overload in PD patients, this outcome has been poorly studied. Woodrow *et al.* observed substantial reductions in systolic blood pressure ( $142 \pm 24$  to  $123 \pm 18$  mmHg), diastolic blood pressure ( $83 \pm 10$  to  $77 \pm 10$  mmHg), antihypertensive medication requirements, bodyweight (by 0.8 kg), and bioelectrical impedance estimates of total body water ( $-1.6$  L) and extracellular water ( $-1.5$  L) within the first month of using icodextrin instead of 2.27% glucose as the daytime dwell in 14 stable CCPD patients.<sup>20</sup> A similar trial in 12 CAPD and five CCPD patients with ultrafiltration failure<sup>21</sup> demonstrated a significant reduction in mean arterial pressure ( $106 \pm 4.0$  to  $96 \pm 4.2$  mmHg,  $P < 0.05$ ) within the first month of icodextrin use. However, bodyweight and plasma albumin concentration were unaffected.

Clinical experience with icodextrin in children is extremely limited. The best available study is a sequential trial by de Boer *et al.* in which 11 children underwent peritoneal dwells with 1.36% glucose, 7.5% icodextrin or 3.86% glucose for 12 h.<sup>22</sup> The ultrafiltration achieved with icodextrin was comparable with that of 3.86% glucose, but significantly greater than with 1.36% glucose. No significant adverse effects were observed over a subsequent 6-week period of polyglucose administration.

#### EXTENSION OF PERITONEAL DIALYSIS TECHNIQUE SURVIVAL BY ICODEXTRIN

There are no randomized or prospective controlled studies addressing this issue. The best published evidence to date that polyglucose may prolong PD technique survival is a retrospective, uncontrolled analysis of icodextrin prescription in 30 CAPD and three CCPD patients with ultrafiltration failure.<sup>23</sup> These patients were mostly high and high-average transporters, had refractory fluid retention despite two hyperosmolar (3.86%/4.25%) glucose bags per day, and were on the verge of haemodialysis transfer because of their ultrafiltration problems. The

prescription of a 12-h icodextrin exchange in lieu of a glucose dwell each day prolonged the death- and transplantation-censored median technique survival by 22 months. A similar retrospective study of icodextrin usage in CAPD patients with ultrafiltration failure observed an extension of technique survival by an average of 1 year.<sup>24</sup> Based on the cost differential between icodextrin-based PD and in-centre haemodialysis, this translated into a saving of approximately £1500 (\$AUD4300) per year of extended PD life. More recently, a prospective uncontrolled Australian study of 12 CAPD and five APD patients with refractory fluid overload demonstrated a mean prolongation of technique survival by 11.6 months (95%CI 6.0–17.3 months).<sup>21</sup> On multivariate Cox proportional hazard model analysis, an extension of technique survival by icodextrin was significantly predicted by a baseline peritoneal ultrafiltration rate of less than 1 L per day. All of these studies were limited by the potentially confounding influences of recall and co-intervention biases. Moreover, none have addressed the equally important question of whether patients with refractory ultrafiltration failure are better off being treated with an icodextrin-based PD regimen or haemodialysis.

#### ICODEXTRIN USE IN PATIENTS WITH DIABETES MELLITUS

The routine use of conventional glucose-based solutions in PD has been linked to a number of adverse metabolic consequences of systemic glucose absorption, including hyperglycaemia, hyperinsulinaemia, hyperlipidaemia, obesity, suppressed appetite and altered food preference.<sup>9–11,25</sup> As icodextrin is a solution containing a spectrum of high molecular weight polysaccharides (average molecular weight 16 200 Da) that are slowly absorbed across the peritoneal membrane, it has been suggested that certain patient groups such as diabetics may benefit from the use of such a non-glucose solution. In the MIDAS study,<sup>13</sup> total carbohydrate absorption during an 8-h dwell was measured in seven controls (six on 3.86% and one on 2.27%), and 11 icodextrin-treated patients. The respective absorptions were 86% ( $62 \pm 5$  g) and 20% ( $29 \pm 5$  g) of the initially infused carbohydrate ( $P < 0.01$ ). Cholesterol, triglyceride and low density lipoprotein (LDL) cholesterol levels fell by 6% to 10% of pretreatment values in the icodextrin group, but these changes did not achieve statistical significance. A subgroup analysis of the 20 (9.6%) diabetic patients in the study showed a similar pattern of changes with respect to ultrafiltration, plasma biochemistry (sodium, chloride, urea, creatinine, phosphate, albumin and osmolality) and symptom profile as in non-diabetic patients. Plasma glucose and glycated haemoglobin levels were not measured, but overall insulin requirements were not different between the two groups. However, a prospective, uncon-

trolled study involving 12 diabetic PD patients treated with icodextrin for impaired ultrafiltration and refractory fluid overload demonstrated a significant improvement in glycaemic control within the first 3 months (mean haemoglobin A1c decreased from  $8.9 \pm 0.7$  to  $7.9 \pm 0.7\%$ ;  $P < 0.05$ ).<sup>21</sup>

When icodextrin is prescribed for diabetic patients, care should be taken to perform blood sugar measurements using a glucose-specific method (e.g. glucose oxidase or hexokinase reference methods). Estimations based on the glucose deshydrogenasepyrroloquinolonequinone (GDH PQQ) method should be interpreted with caution as they may significantly overestimate blood glucose levels because of maltose interference.<sup>26,27</sup> The average error is  $3.6 \pm 1.4$  mmol/L, and has been reported to engender hypoglycaemia through inadvertent excessive insulin administration.<sup>28</sup> Glucometers commonly used in Australia that use the GDH PQQ method include the Advantage, Accucheck and Glucotrend systems (Roche Diagnostics, Sydney, NSW, Australia).

A retrospective case series has also suggested that hyponatraemia complicating icodextrin therapy may be more common in diabetics.<sup>29</sup> The degree of hyponatraemia is usually mild, but may occasionally be severe.

## INCREMENTAL DIALYSIS

Incremental peritoneal dialysis refers to the initial prescription of only one or two daily exchanges for patients with reasonable residual renal function who are commencing renal replacement therapy. The exchange volumes and frequency are subsequently increased to compensate for falls in renal clearance measurements in order to maintain minimal total small solute clearance targets. Icodextrin possesses a number of characteristics, which make it potentially suitable for this type of regimen. These features include its utility in long-dwell exchanges (making it suitable for a convenient single overnight exchange), favourable ultrafiltration profile (providing approximately 3.5 L ultrafiltration and 15 L creatinine clearance per week), and avoidance of peritoneal membrane and systemic glucose exposure.<sup>1</sup> Extensive postmarketing clinical experience would also suggest that such a regimen is relatively safe. However, to date, there have been no formal comparisons of the relative merits of icodextrin and glucose PD solutions in incremental dialysis.

## BIOCOMPATIBILITY

Several *in vitro* and *ex vivo* studies have suggested that icodextrin may offer improved peritoneal membrane biocompatibility compared with conventional glucose-based dialysates by virtue of decreased glucose exposure,

iso-osmolarity and reduced carbonyl stress.<sup>30–38</sup> Short-term clinical studies involving generally small numbers of patients have demonstrated that dialytic small solute clearances and peritoneal transport characteristics remain well-preserved on icodextrin therapy for up to 24 months of follow up.<sup>5,13,14,20,37,39,40</sup> Moreover, a prospective, open-label, randomized controlled trial of 38 CCPD patients in two centres showed that dialysate effluent concentrations of a variety of peritoneal membrane markers (CA125, interleukin-8, carboxyterminal propeptide of type I procollagen and aminoterminal propeptide of type III procollagen) did not differ between glucose- and icodextrin-treated patients over a 2-year period. However, there have been no longer term clinical studies comparing the relative effects of icodextrin and glucose on peritoneal membrane structure or function.

## SAFETY

Numerous clinical studies<sup>5,13–15,20,41</sup> and over 9 years of postmarketing surveillance have confirmed that icodextrin is a safe and well-tolerated osmotic alternative PD solution to glucose. The most significant adverse effect reported to date is a cutaneous hypersensitivity reaction.<sup>42–45</sup> The incidence of skin rashes has been reported in a population of 4045 icodextrin-treated patients to be 2.5%.<sup>10</sup> Most eruptions are psoriasiform in nature, and may be either limited to the palms and soles or extensive with acute generalized exanthematous pustulosis and exfoliation.<sup>46</sup> Although the aetiology is unclear, an immune complex-mediated hypersensitivity reaction appears likely. The use of multiple medications has been a confounding factor in many settings.<sup>42,43</sup>

Another concern raised about the intraperitoneal administration of icodextrin has been the sustained elevation of maltose, maltotriose and other oligosaccharides in the plasma.<sup>13,41,47,48</sup> The rise in plasma oligosaccharide level plateaus after approximately 7 days, and this has led to the recommendation that icodextrin should not be used more frequently than once daily to limit the extent of this increase. The concentrations of icodextrin metabolites in the serum are not appreciably influenced by the presence of diabetes mellitus<sup>13</sup> or peritonitis.<sup>19</sup> After discontinuation of the polyglucose solution, blood levels return to normal within 1–2 weeks,<sup>13,49,50</sup> suggesting that there is no accumulation of maltose in the body. Until now, there have been no clinically apparent adverse effects of elevated plasma maltose and oligosaccharide concentrations. However, elevated maltose levels may interfere with certain assays involved in the measurement of glucose<sup>26,27</sup> and amylase.<sup>51</sup> Caution should, therefore, be observed in the interpretation of the results of such assays in the setting of icodextrin administration.

Peritoneal equilibration test (PET) results have also been shown to be significantly influenced by a preceding

**Table 1** Summary of the advantages and disadvantages of icodextrin relative to glucose-based peritoneal dialysis (PD) solutions

Advantages	Disadvantages
1. ↑ Fluid removal in UFF, particularly: High/high average transporters Diabetics Acute peritonitis	1. Skin rashes 2. Expense (approximately twice cost) 3. Accumulation of maltose and other saccharides
2. ↓ Carbohydrate absorption, better glycaemic control in diabetics	—Interference with biochemical assays (e.g. glucose, amylase)
3. Ultrafiltration maintained over long dwells convenient for incremental dialysis	4. Hyponatraemia (usually mild)
4. ↑ <i>In vitro</i> and <i>ex vivo</i> biocompatibility	
5. ↑ PD technique survival?	

UFF, ultrafiltration failure.

icodextrin exchange. Lilaj *et al.* performed two PETs in each of the 15 PD patients and showed that, compared with 2 L 1.36% glucose dialysate solution, an icodextrin exchange prior to the performance of a PET led to a significant overestimation of the dialysate:plasma creatinine ratio at 4 h.<sup>52</sup> Peritoneal dialysis patients using icodextrin solutions should, therefore, perform their dialysate exchange before a PET with a conventional glucose solution.

Several randomized controlled trials have found that peritonitis rates are not different between icodextrin- and glucose-treated PD patients.<sup>13,41</sup> An *in vitro* study by Choo *et al.* has shown that antibiotics commonly used for the treatment of peritonitis (such as vancomycin, cephalosporins and gentamicin) are compatible and stable with icodextrin.<sup>53</sup>

Finally, icodextrin usage has been associated with slight increases in serum osmolality and falls in serum sodium concentration, which are usually not clinically significant. In the MIDAS trial, serum sodium levels in the icodextrin group fell from  $140 \pm 0.3$  to  $136 \pm 0.3$  mmol/L. Similar changes have been observed in CCPD patients.<sup>41</sup> However, a retrospective analysis by Gradden *et al.* found that diabetic patients were more prone to reductions in serum sodium concentration below the normal range and rarely developed symptomatic hyponatraemia.<sup>29</sup> This has been attributed to a dilutional effect stemming from the flow of water from the intra- to extra-cellular compartments as a result of colloidal osmosis induced by the systemic accumulation of icodextrin and its metabolites. However, other causes of dilutional hyponatraemia (including fluid overload and incipient cardiac failure) may also be operative.

## SUMMARY AND CONCLUSIONS

Icodextrin-containing PD solutions have been shown to be a safe and effective alternative to hypertonic glucose dialysates (Table 1). Ultrafiltration is continuously increased by icodextrin during dwells of up to 16 h. Tak-

ing into account all of its characteristics and the available evidence regarding its use, the patients who are most likely to benefit from this therapy are those with symptomatic fluid overload and ultrafiltration failure, particularly in the settings of acute peritonitis, high transport characteristics, and diabetes mellitus. However, early and continued use of this solution may ultimately prove to be of benefit in many, if not all, peritoneal dialysis patients, and it may become a standard component of peritoneal dialysis therapy. Future, well-designed, prospective clinical trials are needed to evaluate the relative effects of icodextrin and conventional glucose solutions on incremental PD regimens, systemic metabolic sequelae (such as glycaemic control in diabetics), peritoneal membrane structure and function, and PD technique survival (in patients with and without impaired ultrafiltration).

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