Effects of icodextrin on the peritoneal membrane

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Fifteen years after the introduction on the market of a 7.5% icodextrin dialysis solution, its share in a state-of-the-art dialysis prescription has become quite meaningful. This is because of its superiority to induce fluid removal from the body during long dwells, compared to solutions with low-molecular-weight osmotic agents, especially in patients with a fast solute transport status [1,2]. Consequently, the use of icodextrin can effectively reduce over-hydration [3,4]. Although the effects of icodextrin on fluid and solute kinetics are well-known [5–7], issues with respect to inflammation and membrane viability are still unclear. The outbreak of a culture-negative peritonitis in 2001/2002, which was caused by contamination with peptidoglycans [8], raised suspicion that icodextrin could increase susceptibility to local peritoneal inflammation. In a recent abstract presented at the congress of the American Society of Nephrology on factors associated with encapsulating peritoneal sclerosis, the duration of icodextrin treatment was independently associated with this complication [9]. Although this observation is preliminary and should be confirmed in other studies, it was reason to review the old and recent literature on possible effects of icodextrin on the peritoneal membrane.

In vitro studies

Incubation of albumin with icodextrin leads to a reduced formation of the advanced glycosylation end product pentosidine [10], probably due to its low content of glucose degradation products [11]. Studies on biocompatibility have given different results. Icodextrin incubation was associated with reduced viability of peritoneal mesothelial cells, while the phagocytosis capacity of peripheral blood neutrophils was similar to that of conventional glucose/lactate solutions [12]. Other studies have shown better phagocytosis [13,14], less inhibition of cell growth [15] and reduced IL-6 mRNA expression [16]. The general impression of these in vitro studies is that most of them show no indication for a deleterious effect of icodextrin on the peritoneal membrane.

Animal studies

Experimental studies in rodents are often difficult to interpret because these animals have very high plasma— and, therefore, also dialysate—amylose activities. This leads to a faster degradation of icodextrin into its metabolites in the peritoneal cavity than in humans [17,18]. It explains the rise in dialysate osmolality during a dwell with 7.5% icodextrin in rats [19]. It is unknown whether these locally formed oligosaccharides could have effects on peritoneal membrane morphology. Another drawback of animal studies is that they are often performed in animals with normal renal function. These animals may, to some degree, be protected from accumulation of icodextrin degradation products because a part of these will be removed by glomerular filtration, followed by uptake in the proximal tubule and further degradation.
Gotloib et al. described marked mesothelial dysplastic changes and decreased cell viability in a murine model of daily intraperitoneal injections with 7.5% icodextrin for 30 days [20]. The authors hypothesized that the exposure to icodextrin degradation products would cause early cell shrinking due to hyper-osmolality, followed by an increase of cell size caused by cellular uptake of these oligosaccharides. If this would be the trigger, it is unlikely to happen in humans.

A study in our long-term peritoneal exposure model in rats with normal renal function [21] showed that 20 weeks of daily exposure to 7.5% icodextrin was associated with an average of 22 blood vessels per high power field in omental tissue, compared to 35 in animals exposed to a conventional 3.86% glucose/lactate dialysis solution (Zweers et al., unpublished data). Another study was performed in rats with normal renal function in which diabetes mellitus was induced with streptozotocin. These animals were dialysed for a period of 12 weeks with various regimens [22]. The rats dialysed with a glucose-based schedule had the highest staining score for peritoneal advanced glycosylation end products, but the group dialysed with 7.5% icodextrin only had a score similar to that in non-dialysed diabetic animals. Animals exposed to one icodextrin exchange and three glucose exchanges showed accumulation inbetween the glucose- and icodextrin-only group. No evidence for differences in the amount of peritoneal fibrosis was found.

The results of a study by Nakao et al. published in the current issue of Nephrology Dialysis Transplantation [23] extend the results of the one cited above because it was done in diabetic rats with chronic kidney disease induced by 5/6 nephrectomy. Daily intraperitoneal injections were performed for 8 weeks with either a 4.25% glucose solution or 7.5% icodextrin. The animals exposed to the glucose-based solution had the largest number of peritoneal vessels, the widest sub-mesothelial compact zone and the most prominent staining for vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), fibronectin, advanced glycosylation end products (AGE) and the AGE receptor. The icodextrin animals were similar to the non-exposed group with the exception of AGE staining, which was inbetween that of non-exposed and glucose-exposed animals. It can be concluded from the experimental studies that icodextrin exposure is neither associated with marked neoangiogenesis nor with the development of fibrosis. It is uncertain whether it influences mesothelial cell mass.

**Clinical studies**

Studies in patients on parameters of local inflammation and membrane preservation are often difficult to interpret because icodextrin is always used in combination with other, mainly conventional glucose-based solutions. This may dilute possible effects. Only a few single-dwell studies have been published [24,25]. One showed a linear increase in dialysate cancer antigen 125 (CA125) during a 4-h dwell that was similar for a 1.36% and a 3.86% glucose exchange [24]. This gives no indication for acute toxicity of icodextrin on the mesothelium. Another study reported a higher effluent cell count after a 4-h icodextrin exchange (on average 30 × 10⁶ vs 5 × 10⁶/L) in a conventional glucose/lactate-based solution [25]. It may explain the occasional observation of culture-negative peritonitis, also after the peptidoglycan issue was solved [26], because a 3- to 4-fold increase in the cellular content of an icodextrin effluent leads to cloudiness, while for a glucose/lactate-based solution, the increase should be 20-fold to have a similar result. It is unclear whether the higher cell count reflects low-grade inflammation or that it just reflects less inhibition of cell proliferation, as has been shown in the *in vitro* studies.

Longitudinal follow-up of APD patients randomized for a PD prescription, including one icodextrin exchange or not, showed no difference in effluent CA125 between the two groups [27]. A slightly decreasing trend in time was only found for the icodextrin group. No differences or time trends were observed for effluent IL-8. In the same patient cohort, no differences between the two groups were found for effluent concentrations of AGEs and Amadori albumin products [28]. A more recent study in CAPD patients with a follow-up of only 8 weeks also showed no significant effect of icodextrin on effluent CA125 [29]. However, some increases of serum C-reactive protein (CRP) and effluent IL-6 were found. Given the short follow-up in this study, the interpretation of the results should be cautiously done.

The results so far, giving no indication for profibrotic properties of icodextrin, are strengthened by the results of a large randomized controlled trial on the use of a 4% icodextrin solution intraperitoneally in laparoscopic surgery for adhesiolysis. The study was done in patients with normal renal function who had developed adhesions after various, often gynaecological, procedures [30]. The icodextrin group achieved clinical success in significantly more patients than in the placebo group.

**Conclusion**

Assessment of the effects of a 7.5% icodextrin solution on the peritoneal membrane is difficult because it is never used as monotherapy. However, most clinical and experimental evidence suggest that it can be used safely, also on the long-term. No indication has been found that icodextrin has profibrotic properties. Associations with encapsulating peritoneal sclerosis are probably not causal, but may be explained by the indication for its prescription.

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**References**


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