Impact on Peritoneal Membrane of Use of Icodextrin-based Dialysis Solution in Peritoneal Dialysis Patients

Misaki Moriishi, Hideki Kawanishi, Shinichiro Tsuchiya

The usefulness of icodextrin-containing peritoneal dialysis (PD) solution for the management of body fluid and blood pressure has been reported. However, icodextrin PD solution is a foreign solution in the body, and the possible induction of intraperitoneal inflammation has been reported. In this study, we investigated at 6-month intervals the influence of icodextrin solution on peritoneal permeability and inflammatory reactions in patients in whom glucose solution had been changed to icodextrin solution for the overnight dwell.

We enrolled 9 anuric PD patients (5 men, 4 women) of mean age 58 ± 5.9 years (range: 45.6 – 64.8 years) into the study. The patients’ mean duration of PD was 61.9 ± 42 months (range: 6.7 – 142.5 months). The cause of end-stage renal disease was chronic glomerulonephritis in all patients.

For evaluation of peritoneal permeability, we performed peritoneal equilibration tests (PETs) immediately after an overnight dwell and determined the dialysate-to-plasma ratios of creatinine (D/P Cr), β2-microglobulin (D/P β2m), albumin (D/P Alb), immunoglobulin G (D/P IgG), and α2-macroglobulin (D/P α2m). We also measured interleukin-6 (IL-6) and fibrinogen degradation products (FDPs) in overnight effluent as indices of inflammation and of the fibrinolysis–coagulation system. The evaluation was performed every 6 months for 24 months.

The FDPs in effluent increased significantly at 6 months after the change to icodextrin solution, and IL-6 tended to increase. The D/P β2m, D/P Alb, D/P IgG, and D/P α2m all significantly increased in the course of follow-up. In the PETs, the D/P Cr increased slightly, but the change was nonsignificant. At 30 months after the change to icodextrin solution, 1 patient was diagnosed as having a risk of encapsulating peritoneal sclerosis (pre-EPS). In this patient, rapid increases in IL-6, D/P Cr and macromolecular and small molecular D/P by PET were noted after the change to icodextrin solution. Steroids were administered after the diagnosis of pre-EPS, with the result that the IL-6 level rapidly decreased and the D/P Cr and D/P of small molecules and macromolecules slightly decreased.

Icodextrin dialysis solution increased peritoneal permeability. Although the cause was unclear, icodextrin may have changed peritoneal reactivity. Long-term use of icodextrin PD solution requires further investigation.

Key words
Icodextrin, peritoneal permeability

Introduction
Icodextrin solution has become widely used in peritoneal dialysis (PD). Because colloidal osmotic pressure is responsible for transport of water and solutes in dialysis with icodextrin solution (unlike the crystalloid osmotic pressure of glucose solution), a constant volume of water is removed regardless of peritoneal permeability, emphasizing the usefulness of icodextrin for management of body fluid and blood pressure in PD patients. However, the incidence of skin allergy with use of icodextrin solution has been known from the beginning, and increases in the peritoneal leukocyte count and inflammatory products have been reported (1). Thus, concern has arisen that icodextrin solution could induce subclinical intraperitoneal inflammation; however, few reports have addressed the influence of icodextrin solution on peritoneal permeability, and this question has not yet been clarified.
In the present study, we used the dialysate-to-plasma ratio of creatinine (D/P Cr) and of selected macromolecules as determined by a peritoneal equilibration test (PET) using glucose solution after a preceding overnight dwell with icodextrin to evaluate peritoneal permeability. We also evaluated changes in inflammation and the fibrinolysis–coagulation system by measuring interleukin-6 (IL-6) and fibrinogen degradation products (FDPs) in overnight effluent from stable patients on continuous ambulatory peritoneal dialysis (CAPD).

Patients and methods
We enrolled 9 stable CAPD patients (5 men, 4 women), mean age 58 ± 5.9 years (range: 45.6 – 64.8 years), into the study. Their mean duration of PD was 61.9 ± 42 months (range: 6.7 – 142.5 months). The cause of end-stage renal disease was chronic glomerulonephritis in all patients. All patients had been using 4 daily exchanges of 2 L each of glucose-based dialysis solution that was both neutral and low in glucose degradation products (GDPs). No peritonitis occurred in the patients in the 3-month period before the study or during the study period.

Glucose solution for the overnight dwell was changed to icodextrin solution: the dialysis prescription therefore became one exchange of icodextrin solution for the overnight dwell, plus three exchanges of glucose solution during the day. For evaluation of peritoneal permeability, we performed PETs in the patients and calculated D/P Cr, D/P β2-microglobulin (D/P β2m), D/P albumin (D/P Alb), D/P immunoglobulin G (D/P IgG), and D/P α2-macroglobulin (D/P α2m) from serum and the PET effluent. We also measured levels of IL-6 and FDPs in the overnight effluent as indices of inflammation and the fibrinolysis–coagulation system. This evaluation was performed every 6 months for 24 months.

The IL-6 and FDPs in dialysate were measured by chemiluminescent enzyme immunoassay and latex photometric immunoassay respectively. The β2-microglobulin, albumin, and IgG in blood and dialysate were measured by latex agglutination immunoassay. The α2-macroglobulin was measured by nephelometry.

Data are expressed as mean ± standard deviation. The paired-sample t-test was used for statistical analysis, with p < 0.05 defined as significant.

Results
At 6 months after the change to icodextrin solution, FDPs in the overnight dwell increased significantly to 25,830 ± 13,833.8 from 7181.1 ± 2742.4, and IL-6 showed a tendency to increase (Figure 1). In the PETs, the D/P β2m increased significantly to 0.26 ± 0.09 at 24 months from 0.15 ± 0.03 at baseline. The D/P Alb, D/P IgG, and D/P α2m also increased significantly during the course of the study to 0.0210 ± 0.0053 from 0.0147 ± 0.0055 , 0.0129 ± 0.0033 from 0.0088 ± 0.0036, and 0.0049 ± 0.0016 from 0.0034 ± 0.0011 respectively (p < 0.01, p < 0.02, p < 0.02,

![Figure 1](image.png)  
**Figure 1**  Fibrinogen degradation (FD) products and interleukin 6 (IL-6) in overnight effluent.
and $p < 0.03$ respectively; Figures 2 and 3). The D/P Cr also increased slightly, but the change was non-significant (Figure 4).

In the course of the study, a 54-year-old man with a PD duration of 48 months developed ileus symptoms 30 months after the change to icodextrin PD solution. An abdominal computed tomography scan detected edematous intestinal changes, and risk of encapsulating peritoneal sclerosis (pre-EPS) was diagnosed. In this patient, rapid increases in the effluent level of IL-6 and in D/P Cr and macromolecular D/P by PET were noted after the change to icodextrin solution. Steroids were administered after the diagnosis of pre-EPS, and the IL-6 level in effluent rapidly decreased. The PET D/P Cr and macromolecular D/P decreased slightly.

**Discussion**

Icodextrin is manufactured from cornstarch. In rare cases, it induces allergic skin reactions. In Europe,

---

**FIGURE 2** Dialysate-to-plasma (D/P) ratio of $\beta_2$-microglobulin and albumin in overnight effluent.

**FIGURE 3** Dialysate-to-plasma (D/P) ratio of immunoglobulin G and $\alpha_2$-macroglobulin in overnight effluent.
contamination with heat-resistant acidic bacteria (\textit{Alicyclobacillus acidocaldarius}) occurred during the manufacturing process at the beginning of the product’s use. The resulting solutions were contaminated with peptidoglycans produced by the bacteria, and they caused reactive peritonitis in many patients (2–4). In current products, the level of peptidoglycan contamination falls below the measurement limit, but increases in peritoneal leukocyte count and inflammatory products have been reported (5). However, in a large 2-year clinical study, icodextrin solution did not affect peritoneal function any more than a glucose solution with high GDPs (6).

In contrast, a recent study reported by Martikainen et al. (1) investigated icodextrin solution, conventional glucose solution (high GDPs), and amino-acid solution in an 8-week crossover design. When icodextrin solution was used, IL-6 and tumor necrosis factor α increased significantly in effluent. Moreover, the PD duration of the study patients was 1.5 – 6.3 months, suggesting that inflammation was induced in short-term patients, in whom the peritoneum may be normal.

Konings et al. (7) randomly divided patients into icodextrin and conventional glucose (high GDPs) solution groups and found that, after 4 months, \textit{Nε}-carboxymethyl)lysine increased significantly in the blood and dialysate of the icodextrin solution group as compared with those of the conventional glucose solution group. These findings suggested that icodextrin solution induced inflammation.

In a previous study by our group, leukocyte count was significantly increased in long-dwell icodextrin effluent and also increased in glucose solution effluent. Simultaneously measured levels of FDPs also increased, suggesting the persistence of an inflammatory reaction (8). When icodextrin solution was used for the overnight dwell for a prolonged period, and a PET with glucose solution was performed immediately after such a dwell, the ratio of dialysate glucose at the start and end of the dwell \((D/D_0)\) decreased, and the \(D/P\) Cr increased. Those values returned to their previous levels when glucose solution was used preceding a PET (9). Although the mechanisms of these events are unclear, the results suggest that icodextrin induces intraperitoneal inflammation.

The indices of inflammation and of activation of the fibrinolysis–coagulation system increased slightly after our patients were changed to icodextrin solution, and permeability increased for small molecules as well as macromolecules. However, the \(D/P\) Cr determined by a PET using glucose solution did not change. That finding indicates that exposure to icodextrin solution transiently increases peritoneal permeability, but does not induce a morphologic change (such as neovascularization) in the peritoneal blood vessels.

Although the cause is unclear, cases of allergic skin reaction induced by icodextrin PD solution have been reported, suggesting that similar allergic reactions may be occurring in the peritoneum. The changes may have been transient, but long-term exposure may induce changes in vascular morphology and may increase peritoneal permeability, triggering development of EPS. One patient in the present study developed pre-EPS. His duration of PD was intermediate (78 months), and study markers rapidly altered after the change to icodextrin, suggesting an association of icodextrin with a risk of EPS development.

**Conclusions**

Icodextrin dialysis solution increased peritoneal permeability. Although the cause was unclear, icodextrin may have changed peritoneal reactivity. Long-term use of icodextrin PD solution requires further investigation.

**References**

Impact on Peritoneal Membrane of Icodextrin Solution


Corresponding author:
Misaki Moriish, MD, Tsuchiya General Hospital, 3-30 Nakajima-cho, Naka-ku, Hiroshima 730-8655 Japan. E-mail: usagi@tsuchiya-hp.jp