Using changes in cell counts and levels of cancer antigen 125 (CA125), fibrinogen degradation product (FDP), and interleukin-6 (IL-6) in effluent before and after the use of icodextrin-based peritoneal dialysis solution (icodextrin), we evaluated the effects of icodextrin on peritoneal membrane. The subjects were 8 anuric patients (4 men, 4 women) who had been using a 2.5% glucose-based dialysis solution (glucose solution) for the overnight dwell. The mean age of the patients was 57.9 ± 6.1 years, and their mean duration of continuous ambulatory peritoneal dialysis was 61.6 ± 44.3 months. In all patients, chronic glomerulonephritis was the cause of end-stage renal disease.

We changed the 2.5% glucose solution used for the 8-hour dwell to an icodextrin, and we compared cell counts in effluent and levels of IL-6, FDP, and CA125 in the overnight effluent before, and 12 and 36 weeks after, the switch to the icodextrin.

When 2.5% glucose solution was used for the overnight 8-hour dwell, the mean cell count in the effluent was 5.5 ± 3 cells/mm³. However, 12 and 36 weeks after the start of icodextrin, mean cell counts in effluent were significantly increased to 15.3 ± 7.7 cells/mm³ (p < 0.01) and 16.5 ± 11.2 cells/mm³ (p < 0.01) respectively. Values of effluent CA125, FDP, and IL-6 obtained during the use of a glucose solution were compared to values obtained 12 and 36 weeks after the start of icodextrin. Effluent levels of CA125 and IL-6 did not vary before and after the use of the icodextrin, but levels of FDP in the icodextrin effluent were higher than the levels found in the effluent of a 2.5% glucose solution (7278.8 ± 2915 ng/mL before the start of icodextrin; 29,875 ± 13,227 ng/mL 12 weeks after icodextrin introduction, p < 0.01; and 12,062.9 ± 5,684.6 ng/mL 36 weeks after icodextrin introduction).

Icodextrin induced a subclinical inflammatory response in the peritoneum. Therefore, biocompatibility of an icodextrin solution is not always superior to that of a glucose solution, and further research is needed to clarify the influence of long-term icodextrin use on the peritoneum.

Key words
Icodextrin, biocompatibility, leukocyte count, peritoneal membrane, sterile peritonitis

Introduction
Recently, a dialysis solution containing icodextrin as the osmotic agent has been widely used in peritoneal dialysis. Icodextrin-based peritoneal dialysis solution (icodextrin) contains a polyglucose prepared by hydrolysis of starch. The mean molecular weight (MW) of icodextrin is as large as 16,800 Da, and differences in colloid osmotic pressure induce water transport. Because icodextrin is absorbed slowly into the blood, persistent osmotic pressure differences contribute to sufficient ultrafiltration in patients with increased peritoneal membrane permeability, demonstrating the usefulness of icodextrin for the management of body fluid and blood pressure (1). However, the development of allergic dermatologic responses such as erythema, bulla, and exfoliative dermatitis has been reported in 2.5%–15% of PD patients who use icodextrin (2,3). Severe cases of allergic dermatitis (4) and sterile peritonitis (5) have also been reported in association with the use of icodextrin-based solutions. Therefore, the biocompatibility and effects of icodextrin on the peritoneum have become matters of concern.

In the present study, we used changes in cell counts and levels of cancer antigen 125 (CA125), fibrinogen degradation product (FDP), and interleukin-6 (IL-6) in the effluent before and after the use of icodextrin to evaluate the effects of icodextrin on the peritoneal membrane.

Patients and methods
The subjects of the study were 8 anuric patients (4 men, 4 women) who had been using a 2.5% glucose-
based dialysis solution (glucose solution) for the long overnight dwell in continuous ambulatory peritoneal dialysis (CAPD). Their mean age was 57.9 ± 6.1 years (range: 45.2 – 64.1 years), and their mean duration of CAPD was 61.6 ± 44.3 months (range: 5.6 – 140.1 months). In all patients, chronic glomerulonephritis was the underlying disease.

The 2.5% glucose normally used by the patients for an 8-hour overnight dwell was changed to an icodextrin-containing dialysis solution. We compared levels of IL-6, FDP, and CA125 in the overnight effluent, cell count in the effluent, and eosinophil counts in the blood obtained before, and 12 and 36 weeks after, the change to icodextrin.

Results

Cell counts in effluent

We compared cell counts in the daily dialysate (4 bags per day) obtained before icodextrin was started to the counts obtained 12 and 36 weeks after the start of the icodextrin (Figure 1). When a 2.5% glucose-based dialysis solution was used for the overnight dwell, the mean cell count in the effluent was 5.5 ± 3 cells/mm³. Mean cell counts in the effluent obtained 12 and 36 weeks after the start of the icodextrin-based solution were significantly increased to 15.3 ± 7.7 cells/mm³ (p < 0.01) and 16.5 ± 11.2 cells/mm³ (p < 0.01) respectively. After 12 weeks of icodextrin use, the mean cell count in glucose solution used immediately after the icodextrin dwell was significantly increased to 9 ± 1.9 cells/mm³ from 3.5 ± 1.4 cells/mm³ (p < 0.01). However, cell counts in icodextrin effluent and in effluent from other glucose-solution dwells did not increase significantly.

Eosinophil counts in blood

The percentage of eosinophils in the blood obtained before the use of the icodextrin was 6.8% ± 6.2%. That value did not increase at 12 or 36 weeks after the start of icodextrin.

Effluent levels of CA125, FDP, and IL-6

Effluent levels of CA125, FDP, and IL-6 obtained during use of glucose were compared to the levels obtained 12 and 36 weeks after icodextrin was started (Figure 2). Effluent levels of CA125 and IL-6 did not vary before and after the use of icodextrin, but levels of FDP were higher during use of icodextrin than they had been during the earlier use of 2.5% glucose (7278.8 ± 2915 ng/mL with 2.5% glucose; 29,875 ± 13,227 ng/mL 12 weeks after the start of icodextrin, p < 0.01; and 12,062.9 ± 5,684.6 ng/mL 36 weeks after the start of icodextrin).

In patients in whom icodextrin was used from the start of CAPD, white blood cell (WBC) counts in effluent were markedly increased; they decreased when the use of icodextrin was discontinued. However, eosinophil counts in blood did not increase despite the increase in WBC count in the effluent.
Discussion

Icodextrin is primarily useful for managing body fluid and blood pressure, and for improving the quality of life of CAPD patients (1). But because icodextrin is a foreign substance, it is known to induce allergic dermatologic responses from the initial stage of its introduction. The incidence of icodextrin-induced dermatitis is as high as 2.5% – 15%, and the use of icodextrin is restricted in many patients (2–4). Moreover, icodextrin-associated sterile peritonitis occurs in approximately 1% of CAPD patients (2–4). These patients exhibit increased cell counts in effluent, abdominal pain, fever, diarrhea, and vomiting. Patients with icodextrin-associated sterile peritonitis were also reported to show increased cell counts in effluent, reduced neutrophil:monocyte ratios, reduced detection of eosinophils, increased levels of CA125 and inflammatory cytokines (5), and increased levels of monocyte chemoattractant protein 1 (5).

The cause of icodextrin-associated sterile peritonitis has been reported to be contamination of icodextrin with a large quantity of peptidoglycans during the manufacture. However, other reports have suggested that peptidoglycans did not cause the sterile peritonitis, because no increase in CD14 expression was seen in the peripheral and peritoneal macrophages in patients with icodextrin-associated sterile peritonitis (6). The true cause of sterile peritonitis therefore remains unclear.

However, attention has been focused on subclinical intraperitoneal inflammatory responses induced by icodextrin. Parikova et al. reported that increased cell counts in effluent of icodextrin were the result of an inflammatory response directly induced by icodextrin itself, because WBC and eosinophil counts in the effluent did not differ between icodextrin containing a large amount of peptidoglycans and one containing peptidoglycans at a level below 7.5 ng/mL (7). In addition, because CA125 levels did not increase in effluent, the researchers also noted that icodextrin only slightly induced intraperitoneal inflammatory responses and did not deteriorate mesothelial cells (7).

In accord with the results from Parikova et al., our study also showed increased cell counts in the effluent of icodextrin, although the increase fell within the normal range. Furthermore, cell counts increased in the effluent of the glucose-based solution that was used in the exchange immediately after icodextrin. Although the mechanism of this cell increase remains unclear because of the absence of cellular classification, the icodextrin might have induced intraperitoneal inflammation, thus influencing cell counts in effluent during both the icodextrin dwell and the subsequent glucose-solution dwell. Because levels of effluent IL-6 and CA125 did not increase simultaneously, the use of icodextrin only slightly influenced the peritoneum and caused almost no deterioration of the mesothelial cells. However, levels of FDP markedly increased in effluent of icodextrin, suggesting the influence of the inflammatory response on the fibrinolysis system. These findings suggest that icodextrin may induce subclinical inflammatory responses in the peritoneum.

Previously, we reported an increased dialysate-to-plasma ratio of creatinine in peritoneal equilibration tests performed after a dwell with icodextrin (8). If
subclinical inflammatory responses secondary to exposure to icodextrin contribute to that phenomenon, the inflammatory response induced by icodextrin may increase peritoneal blood flow and peritoneal membrane permeability to small molecules. Further work is needed to address these problems.

**Conclusions**

Icodextrin induced a subclinical inflammatory response in the peritoneum. However, whether this inflammatory response is directly induced by icodextrin or by a small amount of peptidoglycans in the icodextrin remains unclear. However, biocompatibility of icodextrin is not always superior to that of glucose solution, and further research is needed to clarify the influence on the peritoneum of long-term use of icodextrin.

**References**


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