

A Case of Encapsulating Peritoneal Sclerosis Suspected to Result from the Use of Icodextrin Peritoneal Solution

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Encapsulating peritoneal sclerosis (EPS) is an intestinal obstruction syndrome in which peritoneal deterioration and intraperitoneal inflammation result in intestinal adhesions, which are covered with a fibrin capsule and which cause bowel obstruction.

Here, we report the case of a patient with EPS suspected to result from the use of icodextrin peritoneal solution. In this patient, peritoneal permeability to high molecular weight solutes and effluent interleukin-6 (IL-6) levels increased after initiation on-to icodextrin solution. The patient developed symptoms of intestinal obstruction accompanied by intestinal edema 30 months after the start of icodextrin and after a peritoneal dialysis (PD) duration of 78 months. He was then diagnosed as being in a pre-EPS state. The use of icodextrin solution was discontinued, and the symptoms of intestinal obstruction improved after corticosteroid administration. Subsequently, he was managed on a combination of PD using glucose solution low in glucose degradation products and of twice-weekly hemodialysis, but he showed enhanced peritoneal permeability and increases in effluent IL-6. After a PD period of 98 months, severe symptoms of intestinal obstruction developed, and enterolysis was performed. The degeneration of the intestinal wall itself was slight, and the adhesions between the capsule and intestinal surface could be readily removed.

In this patient, the degree of peritoneal deterioration and capsule formation differed from that of typical EPS. These findings suggest the promotion of capsule formation by icodextrin

solution and the involvement of certain inflammatory reactions.

Key words

Encapsulating peritoneal sclerosis, icodextrin, peritoneal permeability, IL-6

Introduction

Encapsulating peritoneal sclerosis (EPS) develops when peritoneal dialysis (PD) causes peritoneal deterioration and when a capsule formed by accumulated fibrin covers the deteriorated intestine and becomes firm, thereby impairing intestinal peristalsis, leading to the appearance of bowel obstruction symptoms (1).

Icodextrin peritoneal solution has become widely used in PD. Because colloidal osmotic pressure is responsible for the 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 the management of body fluid and blood pressure in PD patients (2). However, the incidence of skin allergy with the use of icodextrin solution has been known from the beginning, and increases in the peritoneal leukocyte count and the presence of products of inflammation have been reported (3). Thus, concern has arisen that icodextrin solution may induce subclinical intraperitoneal inflammation. Few reports have addressed the influence of icodextrin solution on peritoneal permeability, however, and this question has not yet been clarified.

No studies have yet been conducted on the direct association between icodextrin solution and development of EPS. Here, we report the case of a patient with EPS suspected to result from the use of icodextrin peritoneal solution.

Case report

A 51-year-old man with chronic glomerular nephritis started continuous ambulatory PD (CAPD) treatment using 3×1.5-L dwells of 1.5% glucose (Dianeal: Baxter Healthcare, Tokyo, Japan) in March 1999. A fast peritoneal equilibration test (PET) immediately after PD introduction showed a stable 0.53 dialysate-to-plasma (D/P) ratio of creatinine (Cr). Subsequently, the patient was managed with 4×1.5-L dwells of 1.5% glucose, but his urine volume declined to 100 mL daily in June 2002 (anuria). An ultrafiltration volume (UFV) of 1800 mL daily was obtained with 3×2.0-L dwells of 2.5% glucose and 1×2.0-L dwell of 1.5% glucose. In May 2003, the use of icodextrin solution (Extraneal: Baxter Healthcare) and neutral-pH glucose solution [low in glucose degradation products (GDPs)—Dianeal-N: Baxter Healthcare] was initiated, and an UFV of 1000 mL daily was obtained with an 8-hour 2.0-L dwell with Extraneal and 3×2.0-L dwells of 2.5% glucose. A PET immediately before the initiation of icodextrin showed a D/P Cr of 0.50 and D/P ratios for the macromolecules β_2 -microglobulin, albumin, immunoglobulin G (IgG), and α_2 -macroglobulin of 0.13, 0.012, 0.0093, and 0.003 respectively in the overnight dwell. The effluent fibrin or fibrinogen degradation products (FDPs) and interleukin 6 (IL-6) levels in the overnight dwell were 13.9 pg/mL and 6400 ng/mL respectively. After the initiation of icodextrin, the D/P Cr by PET, the D/P ratios of macromolecules in the overnight dwell, and the effluent IL-6 level showed gradual increases (Figures 1 and 2).

In July 2005, 30 months after the initiation of icodextrin solution (total PD duration: 78 months), intestinal obstruction developed. Computed tomography (CT) of the abdomen revealed edematous intestinal changes, suggesting the risk of EPS. The PET immediately before the appearance of this symptom showed enhanced permeability (D/P Cr of 0.83 and macromolecular D/P ratios for β_2 -microglobulin, albumin, IgG, and α_2 -macroglobulin of 0.39, 0.022, 0.012, and 0.0041 respectively in the overnight dwell) and an increased effluent IL-6 level (112 pg/mL). However, the level of effluent FDPs was unchanged (4560 ng/mL). The level of C-reactive protein (CRP), which had changed to about 0.12 mg/dL from 0.05 mg/dL, increased slightly (0.35 mg/dL) with the development of the intestinal obstruction symptoms. After administration of prednisolone (0.5 mg/kg daily), the intestinal obstruction symptoms and abdominal CT findings improved. However, the D/P Cr by PET, the macromolecular D/P

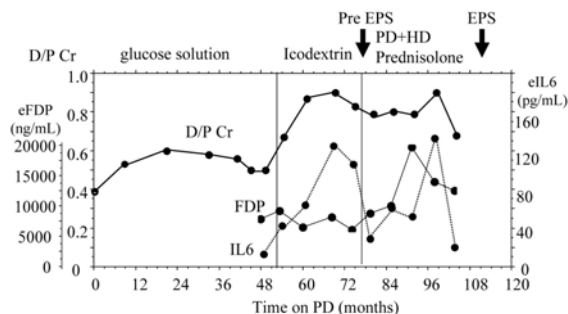


FIGURE 1 Changes in effluent interleukin 6 (eIL6) and effluent fibrin degradation products (eFDP) from the overnight dwell and in dialysate-to-plasma creatinine (D/P Cr) in a peritoneal equilibration test. EPS = encapsulating peritoneal sclerosis; PD = peritoneal dialysis; HD = hemodialysis.

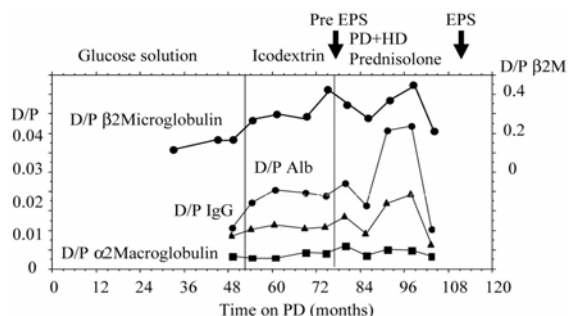


FIGURE 2 Changes in macromolecular dialysate-to-plasma (D/P) ratios of β_2 -microglobulin (β_2 M), albumin (Alb), immunoglobulin G (IgG), and α_2 -macroglobulin in the overnight dwell. EPS = encapsulating peritoneal sclerosis; PD = peritoneal dialysis; HD = hemodialysis.

ratios of β_2 -microglobulin, albumin, IgG, and α_2 -macroglobulin in the overnight dwell, and the effluent level of FDPs remained high. Subsequently, the patient was treated with a combination of CAPD, using 2×2-L dwells of neutral-pH glucose solution, and twice-weekly hemodialysis.

In April 2008, however, the patient developed intestinal obstruction symptoms (duration of PD: 98 months; Figure 3) and underwent total enterolysis. Laparotomy was performed on 26 June 2008. The small intestine showed no cocooning, but its entire surface was covered with a thick capsule, and bending and stenosis were observed inside (Figure 4). However, the

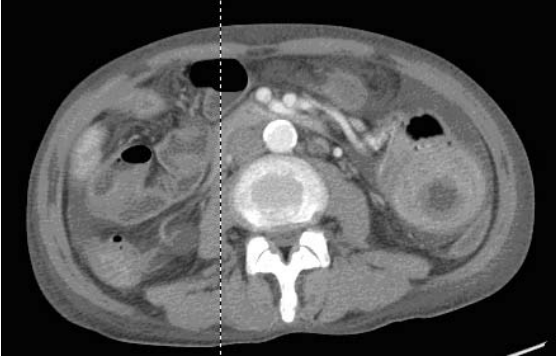


FIGURE 3 Findings of abdominal computed tomography in fully developed encapsulating peritoneal sclerosis.

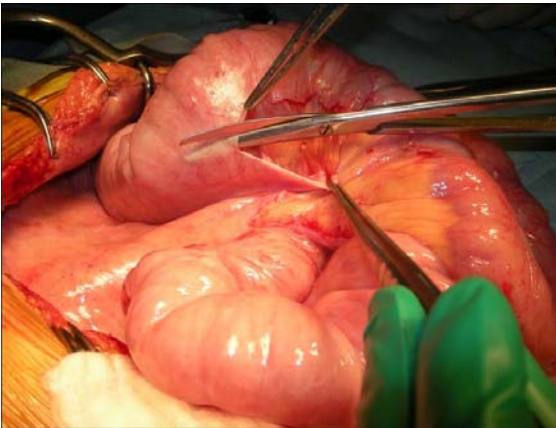


FIGURE 4 The surgical findings in fully developed encapsulating peritoneal sclerosis.

degeneration of the intestinal wall itself was slight, and adhesions between the capsule and the intestinal surface could be readily removed. After resection of the entire capsule, the small intestine was fixed using Noble plication (4). Pathology examination of the parietal peritoneum showed a thin compact zone and light fibrosis, with remaining mesothelial cells. As of March 2009, the patient's postoperative condition remains stable without recurrence.

Methods

The fast PET is performed after an 8-hour dwell with 2.5% glucose solution. Overnight effluent data were

obtained from glucose solution (not icodextrin). The IL-6 and FDPs in overnight effluent were measured by chemiluminescent enzyme immunoassay and latex photometric immunoassay respectively. The β_2 -microglobulin, albumin, IgG, and α_2 -macroglobulin in plasma and effluent were measured by latex agglutination immunoassay and nephelometry respectively.

Discussion

Encapsulating peritoneal sclerosis develops when PD therapy (mainly with bioincompatible dialysis solutions) causes peritoneal deterioration, and a capsule formed by accumulated fibrin covers the deteriorated intestine and becomes firm, thereby impairing intestinal peristalsis, leading to the appearance of bowel obstruction symptoms (1). The desquamation and disappearance of peritoneal mesothelial cells because of long-term exposure to PD solutions results in the progression of peritoneal fibrosis. In addition, peritoneal capillary angiogenesis and hyperplasia develop, increasing peritoneal permeability (5). The new blood vessels appear to exhibit abnormally increased endothelial permeability to high molecular weight substances such as fibrin (1). In this manner, a fibrin membrane is formed on the surface of a thickened, fibrotic peritoneum. In addition, complicating episodes of inflammation, particularly as a result of bacterial peritonitis, further increase peritoneal permeability and cause the deposition of large amounts of fibrin, leading to rapid capsule formation and EPS.

Inflammation is involved in the mechanism of EPS development. Not only acute inflammation, such as bacterial peritonitis, but also mild, persistent inflammation can cause EPS. In particular, the influence of dialysis solution is important because of its continuous use.

Icodextrin is manufactured from cornstarch. In rare cases, it induces allergic skin reactions. In Europe, contamination with heat-resistant acidic bacteria (*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 those compounds caused reactive peritonitis in many patients (6). In current products, the levels of peptidoglycan contamination fall below the measurement limit, but increases in peritoneal leukocyte count and products of inflammation have been

reported (7). However, in a large 2-year clinical study, icodextrin solution had no more effect on peritoneal function than did a glucose solution high in GDPs (8).

In contrast, a recent report by Martikainen *et al.* (3) investigated icodextrin solution, conventional glucose solution (high in 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 these short-term patients, in whom the peritoneum may be normal. Konings *et al.* (9) randomly divided patients into groups using either icodextrin or conventional glucose (high in GDPs) solution and found that, after 4 months, N_{ϵ} -carboxymethyllysine increased significantly in the blood and dialysate of the icodextrin solution group as compared with the conventional glucose solution group. These findings suggest that icodextrin solution induces inflammation.

In a previous study by our group, leukocyte count and FDP levels were significantly increased in long-dwell icodextrin effluent (10). 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 (11). Moreover, IL-6 and FDPs in effluent and peritoneal permeability increased after a change to icodextrin solution (12).

Although the cause is unclear, cases of allergic skin reaction induced by icodextrin 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 the development of EPS.

The patient reported here showed rapid increases in effluent IL-6, D/P Cr, and macromolecular D/P ratios after the use of icodextrin for 30 months, and he developed EPS symptoms. Although the symptoms improved after discontinuation of icodextrin solution and treatment with steroids, they gradually progressed thereafter, requiring surgery. Surgery revealed a soft intestine and slight peritoneal degeneration (unlike typical EPS), with capsule formation covering the intestinal folds. Pathology examination of the parietal peritoneum confirmed mild fibrosis and remaining

mesothelial cells. This difference between the degree of peritoneal degeneration and that of capsule formation suggests the promotion of capsule formation. The slight peritoneal degeneration meant that enterolysis was straightforward, and the patient's postoperative condition remains stable, without recurrence. Inflammation may be involved in the promotion of capsule formation, suggested by the difference between the degree of peritoneal degeneration and that of capsule formation—different from that of typical EPS (13).

In this patient, before the development of the pre-EPS state, permeability to high molecular weight solutes was enhanced, and the effluent level of IL-6 was increased. Effluent FDPs were not elevated in the pre-EPS stage, but they subsequently increased. That finding suggests inflammation and an associated enhancement of peritoneal permeability and fibrin formation as the mechanism of EPS development. There was a time difference between the increase in effluent IL-6 and that in effluent FDPs. Whether this difference indicates stages in the development of EPS or is associated with the use of icodextrin solution remains unclear. Previous studies have shown an association between effluent IL-6 or FDPs and enhanced peritoneal permeability (14). The clinical course of our patient suggests that increases in these substances are risks for EPS.

Conclusions

In a patient with EPS suspected to result from the use of icodextrin solution, the degree of peritoneal deterioration differed from the degree of capsule formation, which was different from typical EPS. This finding suggests the promotion of capsule formation by icodextrin solution and the involvement in EPS of certain inflammatory reactions.

References

- 1 Dobbie JW. Pathogenesis of peritoneal fibrosing syndromes (sclerosing peritonitis) in peritoneal dialysis. *Perit Dial Int* 1992;12:14–27.
- 2 Wolfson M, Piraino B, Hamburger RJ, Morton AR, on behalf of the Icodextrin Study Group. A randomized controlled trial to evaluate the efficacy and safety of icodextrin in peritoneal dialysis. *Am J Kidney Dis* 2002;40:1055–65.
- 3 Martikainen TA, Teppo AM, Gronhagen-Riska C, Ekstrand AV. Glucose-free dialysis solutions: inducers of inflammation or preservers of peritoneal membrane? *Perit Dial Int* 2005;25:453–60.

- 4 Kawanishi H, Ide K, Yamashita M, *et al.* Surgical techniques for prevention of recurrence after total enterolysis in encapsulating peritoneal sclerosis. *Adv Perit Dial* 2008;24:51–5.
 - 5 De Vriese AS, Tilton RG, Stephan CC, Lameire NH. Vascular endothelial growth factor is essential for hyperglycemia induced structural and functional alterations of the peritoneal membrane. *J Am Soc Nephrol* 2001;12:1734–41.
 - 6 Martis L, Patel M, Giertych J, *et al.* Aseptic peritonitis due to peptidoglycan contamination of pharmacopoeia standard dialysis solution. *Lancet* 2005;365:588–94.
 - 7 Parikova A, Zweers MM, Struijk DG, Krediet RT. Peritoneal effluent markers of inflammation in patients treated with icodextrin-based and glucose-based dialysis solutions. *Adv Perit Dial* 2003;19:186–90.
 - 8 Davies SJ, Brown EA, Frandsen NE, *et al.* Longitudinal membrane function in functionally anuric patients treated with APD: data from EAPOS on the effects of glucose and icodextrin prescription. *Kidney Int* 2005;67:1609–15.
 - 9 Konings CJ, Schalkwijk CG, van der Sande FM, Leunissen KM, Kooman JP. Influence of icodextrin on plasma and dialysate levels of N_ε-(carboxymethyl)lysine and N_ε-(carboxyethyl)lysine. *Perit Dial Int* 2005;25:591–95.
 - 10 Moriishi M, Kawanishi H, Tsuchiya S. Impact on peritoneal membrane of use of icodextrin-based dialysis solution in peritoneal dialysis patients. *Adv Perit Dial* 2006;22:24–8.
 - 11 Moriishi M, Kawanishi H, Watanabe H, Tsuchiya S. Effect of icodextrin-based peritoneal dialysis solution on peritoneal membrane. *Adv Perit Dial* 2005;21:21–4.
 - 12 Moriishi M, Kawanishi H. Icodextrin and intraperitoneal inflammation. *Perit Dial Int* 2008;28(Suppl 3):S96–100.
 - 13 Kawanishi H, Watanabe H, Moriishi M, Tsuchiya S. Successful surgical management of encapsulating peritoneal sclerosis. *Perit Dial Int* 2005;25(Suppl 4):S39–47.
 - 14 Moriishi M, Kawanishi H. Fibrin degradation products are a useful marker for the risk of encapsulating peritoneal sclerosis. *Adv Perit Dial* 2008;24:56–9.
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