Icodextrin-associated peritonitis: what conclusions thus far?

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Introduction

Icodextrin 7.5% (Extraneal; Baxter Healthcare, McGaw Park, IL, USA) is an iso-osmolar formulation of maltodextrin glucose polymer derived from starch that is increasingly used to enhance ultrafiltration during long dwells in continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) patients [1–3]. Since its introduction in the UK in 1994, icodextrin has been used in more than 23 000 patients in many parts of the world [4]. Except for rare cutaneous hypersensitivity reactions [5,6], icodextrin is generally safe and well tolerated. Within the last 3 years, however, several reports of sterile chemical peritonitis have been attributed to icodextrin prescription [7–19]. In this comment, we will briefly review the clinical and physiopathological aspects of this syndrome.

Clinical presentation of icodextrin-associated peritonitis

Typically, peritoneal dialysis (PD) patients with icodextrin-associated sterile peritonitis are admitted with abdominal discomfort and cloudy dialysate effluents. No associated rash, fever or other hypersensitivity
manifestations are present. Many patients have noticed that dialysate effluents were mainly cloudy under icodextrin and that they progressively cleared under glucose-based solutions [14,19]. Cell count in the effluent varies from 100 to 3500 white blood cells/µl [14]. It shows a predominance of mononuclear cells (macrophages and/or monocytes) [14], although neutrophils and lymphocytes have also been identified [12]. An excess of eosinophils has also been reported in some patients [14,17]. Most importantly, all dialysate cultures remain sterile, even in enriched media [12–15,19]. Usually, icodextrin has to be discontinued to clear the dialysate effluents, although we have observed that symptoms may progressively subside in a few cases despite maintenance of icodextrin prescription [14]. In addition, re-challenge often results in re-appearance of cloudy dialysates within a few days [7,8,12–14].

The delay between initiation of icodextrin and the first symptoms ranges from a few hours, i.e. the first exchange [7,8], to several months [9,11,14]. Finally, the symptoms may also occur in the resolution phase of an infectious peritonitis [10–11,16].

**What is the prevalence of the syndrome?**

Williams and Foggensteiner [12] initially reported the occurrence of these symptoms in 20% (3/15) of their patients exposed to single exchanges of icodextrin in an early-start dialysis programme. Subsequently, the same group extended their series with an incidence of 46% (12/26 patients) [15]. We found nine such cases in our icodextrin-using population of 104 patients (8.7%) [14], whereas MacGinley et al. [13] reported a prevalence of 4.3% (6/141 patients). It is likely that this prevalence is underestimated because of the absence of clinical symptoms and/or of detection of cloudy dialysates in some patients. The fact that, on APD, the presence of cloudy dialysates is less easily detected probably explains the clustering of this entity in CAPD patients.

**What are the consequences?**

At admission, the vast majority of patients has been initially diagnosed as having an infectious peritonitis and was given empirical antibiotics. Catheter removal has even been performed in a few patients in whom a diagnosis of relapsing peritonitis was made [12,19]. A diagnosis of peritoneal reaction to icodextrin is thus of great importance to avoid unnecessary manoeuvres.

It has been suggested recently that patients with sterile peritonitis secondary to icodextrin have less severe peritoneal inflammation than patients with infectious peritonitis [17]. This was supported by a weight gain, an increase in peritonitis-associated peritoneal permeability, a serum C-reactive protein level, and a leukocyte number in peritoneal dialysis effluent that were all lower in the former than in the latter group [17].

Despite this preliminary report [17], several lines of evidence suggest that sterile chemical peritonitis secondary to icodextrin is not a benign event. Several manifestations of acute peritoneal inflammation including mesothelial desquamation, presence of fibrin clusters on the peritoneal surface and oedema, together with a marked cellular infiltration of the connective tissue by lymphocytes, few polymorphonuclear neutrophils, eosinophils and mast cells were identified in the first peritoneal biopsy from a patient with a typical symptomatology [18]. Immunoperoxidase staining demonstrated that the infiltrating cells were mostly macrophages and T-lymphocytes. All these features are different from those found in bacterial peritonitis [20]. In this patient who had several bouts of sterile peritonitis, the peritoneal transport characteristics remained virtually unchanged, and the peritoneal biopsy did not show any signs of peritoneal fibrosis, suggesting that the peritoneal inflammatory lesions were acute [18]. We now have additional data on two other peritoneal biopsies (patients 3 and 4, table I in ref. 14) taken at the time of catheter removal for pleuroperitoneal communication and renal transplantation, respectively (both patients were still be given icodextrin despite several episodes of cloudy dialysates). Varying degrees of peritoneal inflammation characterized by venulitis and/or submesothelial inflammation displaying abundant T lymphocytes and macrophages were observed, confirming the hypothesis that peritoneal inflammation of the icodextrin-associated peritonitis is not so benign. Macrophages and variable amounts of mast cells were also found throughout the interstitial peritoneal tissue. In contrast, no similar lesions, except for long-term PD changes and rare interstitial macrophages, were seen in control biopsies from two long-term PD patients on icodextrin for >2 years who never had sterile peritonitis (E. Goffin et al., manuscript in preparation).

**What is the cause of this syndrome?**

The cause of the chemical peritonitis secondary to icodextrin has recently been identified [21]: according to the manufacturer, certain batches of icodextrin bags contained varying amounts of peptidoglycan, as a contaminant. Peptidoglycans are major components of the Gram-positive cell wall [22]; like endotoxins, peptidoglycans have many biological activities including the ability to release pro-inflammatory cytokines from mononuclear cells [23]. This latter point is thus likely to explain both the occurrence of cloudy dialysate effluents observed under icodextrin and the presence of the mononuclear cell infiltration within the peritoneal membrane.

It is of note that this theory of the peptidoglycans, although reasonable and probably acceptable, has been provided by the icodextrin manufacturer, without proof coming from independent researchers.
Unanswered questions

After identification of peptidoglycan as the cause of the syndrome, all icodextrin batches suspected to contain an elevated peptidoglycan level were recalled by the manufacturer. This recall led to a dramatic reduction in the occurrence of sterile peritonitis, but not its complete disappearance. For instance, the peritoneal inflammation illustrated in Figure 1 occurred while this patient was given icodextrin dialysates with a peptidoglycan level below the threshold for recall (Baxter Healthcare, personal communication). Likewise, Enia et al. [16] recently reported on a patient with an earlier history of cloudy dialysate attributed to icodextrin presenting recurrence of abdominal discomfort and cloudy dialysate immediately after the first use of new batch of icodextrin. Taking this into account, it may be that some patients could become ‘allergic’ to either icodextrin or to a small residual amount of peptidoglycan present in the icodextrin dialysate. This would explain some positive skin tests [17] and the peritoneal biopsies of our patients suggestive of a hypersensitivity reaction [18].

Conclusions and recommendations

Undoubtedly, the use of icodextrin in CAPD and APD patients has numerous advantages over glucose-based dialysates including improved ultrafiltration, better fluid control and less hypertension [24], decreased exposure to glucose and probably increased technique survival. In the face of evident benefits, clinicians should, however, be aware of the potential of icodextrin to induce chemical sterile peritonitis. In patients in whom such a diagnosis is plausible (by definition, dialysate culture has to be sterile), icodextrin should be withdrawn immediately because our histology cases did not show benign lesions. In patients in whom the icodextrin prescription is mandatory, a re-challenge could be performed within 2–4 weeks after the dialysate effluent has cleared. If cloudy dialysate reappears, icodextrin must then be definitely withdrawn. If contamination of icodextrin by peptidoglycan is really the cause of this syndrome, the recall of contaminated batches should be reflected by a dramatic decrease in its incidence in the near future. Still, the use of peptidoglycan in animal models of peritoneal dialysis, or for skin tests in ‘allergic’ patients could however put arguments forward into the debate. This latter approach could clarify if an ‘allergic’ reaction restricted to the peritoneal membrane is the cause of the recurrence of the symptoms in some patients and if a therapeutic intervention could allow those patients to further resume icodextrin infusion.

Finally, these cases illustrate the importance of the manufacturing process of peritoneal dialysis fluids given the extreme reactivity of the peritoneal membrane. They also provide new insights into the various inflammatory states that may affect the peritoneal membrane longevity.

Conflict of interest statement. None declared.

References