Encapsulating peritoneal sclerosis and other aspects of long-term peritoneal dialysis

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Chapter 1

GENERAL INTRODUCTION
Peritoneal dialysis

Peritoneal dialysis (PD) is a well established modality of renal replacement therapy (RRT). In PD, dialysis fluid is instilled in the abdominal cavity through a surgically implanted catheter. This fluid contains an osmotic agent, mostly glucose, which provides an osmotic gradient for the removal of waste products and excess water from the circulation into the peritoneal cavity via diffusion and convection. When after several hours equilibrium is reached, the saturated dialysis fluid is drained from the abdominal cavity. This cycle of installation and drainage of dialysis fluid must be repeated several times a day. In 2007, over 13,000 patients required RRT in The Netherlands, of which little over 1700 patients were incident patients. The percentage that received PD was almost 23% \(^1\). Overall patient survival is similar for PD and hemodialysis \(^2\) but the first years of dialysis, a survival advantage seems to be present for patients treated with PD \(^3\).

Long-term peritoneal dialysis

Long-term PD is associated with functional and structural alterations of the peritoneum. The peritoneal membrane may lose its ultrafiltration capacity over time \(^4,5\), as a result of which patients have to switch to another form of RRT. Structural changes include fibrosis and sclerosis of the peritoneum \(^6,7\). The bioincompatible nature of conventional peritoneal dialysis fluids (PDF) is thought to play a key role in the development of peritoneal alterations during chronic PD. Conventional PDFs are considered bioincompatible due to their acidic pH, lactate buffer, high concentrations of glucose, and glucose degradation products (GDP) formed during heat sterilization. Several \textit{in vitro} studies have associated these characteristics with peritoneal cell toxicity \(^8,9\). Moreover, both animal \(^10-12\) and clinical \(^13\) studies have shown that long-term exposure to bioincompatible dialysis solutions induces peritoneal changes, such as an increase in peritoneal solute transport over time and the development of fibrosis and neoangiogenis.

Nowadays, more biocompatible PDFs are on the market. One of the most noteworthy improvements has been the development of a multicompartimental bag system that allows glucose to be sterilized at a low pH to minimize GDP formation during sterilization \(^14\). Also the replacement of lactate buffer with bicarbonate has been a major improvement because of its neutral pH that prevents inflow pain in PD patients \(^15\). Until now, it has not been possible to fully replace glucose as an osmotic agent; therefore, the development of more biocompatible dialysis solutions remains an ongoing challenge.
Encapsulating peritoneal sclerosis

Encapsulating peritoneal sclerosis (EPS) is the most serious complication of long-term PD. Bowel loops are entrapped in a dense cocoon of fibrous tissue leading to repeated bowel obstruction. It is accompanied by high morbidity and mortality rates. Several hypotheses on the mechanisms leading to EPS, for example the “two-hit theory,” have been postulated over time but there is still a gap in the current knowledge about peritoneal pathology and EPS. The Peritoneal Biopsy Study Group found evidence in patients that uremia is related to both fibrotic and vascular changes of the peritoneum. Long PD duration, chronic exposure to conventional, bioincompatible, glucose-based PDFs, and recurrent peritonitis episodes may lead to peritoneal fibrosis and sclerosis but only a few of these patients develop EPS. Receiving a kidney transplant as well as a genetic contribution or predisposition have been suggested to be involved in the development of EPS. All the previously mentioned factors are summarized in Figure 1.

Figure 1 – This figure illustrates the mechanisms involved in the development of encapsulating peritoneal sclerosis (EPS). The exact mechanism remains unknown. PDFs = peritoneal dialysis fluids.
Accurate diagnosis of this severe disease is very important. The diagnosis is based on clinical symptoms, such as abdominal pain, nausea, vomiting, repeated bowel obstruction, blood-stained effluent, and loss of ultrafiltration capacity, in combination with pathological findings and abdominal imaging. Imaging techniques are helpful in diagnosing EPS but, unfortunately, no screening methods are available yet. There is no need to stop long-term PD without the presence of symptoms indicating the development of EPS and whether or not to discontinue PD therapy should be judged per patient. Although it is a rare condition, it remains a topic of great interest due to its severity.

Animal models for peritoneal dialysis

Almost a century ago, Tracy Jackson Putnam was the first to describe the living peritoneum as a dialyzing membrane in cats, dogs and rabbits. He discovered that water and solutes diffused through the peritoneum both from and to the bloodstream in such a way that solutions inserted in the peritoneal cavity came in equilibrium with blood plasma. Sheep have also been used in experimental PD to study lymphatic removal of dialysate from the peritoneal cavity. Nowadays, mainly mice and rats are used to study effects of PD and therapeutic strategies.

A variety of experimental PD models have been developed. Acute models with a single peritoneal dwell, peritonitis models, fibrosis and sclerosis models, genetically modified models, and chronic peritoneal infusion models. The latter are of importance in studying long-term effects of PD. These models vary in open or closed peritoneal catheter systems, the absence or presence of renal failure, and the duration of exposure to PDFs. To test new, more biocompatible dialysis solutions, chronic models have been valuable. Models of simple peritoneal sclerosis and EPS are frequently based on local administration of chemical irritants to induce sclerosis and encapsulation. No studies of models based on chronic exposure to bioincompatible PDFs in combination with a state of renal failure to mimic the clinical situation have been published.

The chronic peritoneal infusion model that is currently used by our research group consists of a closed catheter system (Figure 2), a one-step 70% nephrectomy to induce renal failure (Figure 3), and 16 weeks of peritoneal exposure. After 16 weeks of exposure, a peritoneal permeability analysis adapted for the rat is performed. This peritoneal permeability test is comparable to those in humans and provides information on peritoneal transport characteristics. At the end of the experiment, peritoneal tissues are obtained for histological examinations.
The main goals of animal experiments in PD are preservation of the peritoneal membrane and improvement of patient outcome. There is a continuing need for animal experiments to better understand the pathophysiology of the peritoneal membrane, to investigate functional and morphological changes induced by PD, and to test new dialysis solutions or therapeutic interventions for PD complications.

Figure 2 – Catheter implantation: a catheter is inserted in the peritoneal cavity and tunneled subcutaneously to the neck where an access port (Rat-o-Port) is attached, to allow daily infusion of a dialysis solution for a prolonged period in awake animals.

Figure 3 – One-step 70% nephrectomy: The right kidney is removed in total and based on its mass, part of the upper and lower pole of the left kidney is removed to create a 70% nephrectomy.
Outline of the thesis

The first part of this thesis focuses on long-term effects of PD in patients and particularly on EPS. Chapter 2 describes a study in which computed tomographic (CT) findings of EPS patients were compared to those of long-term PD patients without EPS. The aim was to identify CT features characteristic for EPS to enable accurate diagnosis of this disease. Chapter 3 provides an overview of all imaging techniques that have been applied in diagnosing EPS. Qualities and shortcomings of these imaging modalities are discussed in this chapter. In Chapter 4, a case of a patient with Alport syndrome who was treated with biocompatible PDFs exclusively and developed EPS is discussed. A careful suggestion that Alport syndrome may increase the susceptibility of the peritoneal membrane for fibrosis and sclerosis is done. Chapter 5 evaluates possible relations of peritoneal calcifications seen in long-term PD to aortic calcifications and disturbances in mineral metabolism. The patients were divided into two groups based on the presence or absence of peritoneal calcifications assessed by CT scanning. The presence and severity of abdominal aortic calcifications were also assessed by CT scanning. The aortic calcification scores as well as plasma calcium, phosphorus and PTH levels were compared between patients with and without peritoneal calcifications.

Long-term experimental PD is the topic of the second part of this thesis. In Chapter 6, the hydroxyproline content of peritoneal effluent of rats with normal renal function and renal failure, with or without exposure to PDFs, is investigated as marker for peritoneal fibrosis. Chapter 7 and Chapter 8 describe two attempts to develop a new rat model of peritoneal sclerosis. Rats with renal failure exposed to bioincompatible PDFs formed the basis of these two studies. Chapter 9 contains a study in which rats with normal renal function were exposed to a conventional heat-sterilized solution or filter-sterilized solution (without GDPs) and compared to rats that were exposed to an experimental, more biocompatible pyruvate-buffered solution with a combination of three osmotic agents for a period of 20 weeks. Another experimental, more biocompatible solution (GLAD) is subject of Chapter 10 and Chapter 11. First, this solution was tested in rats with renal failure and compared to a conventional solution as well as to a glucose-free buffer. Thereafter, the possible role of nitric oxide on fast peritoneal transport induced by GLAD was investigated. Finally, Chapter 12 contains the summary and discussion of this thesis, and suggestions for future investigations are made.
References

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