Pharmacological modulation of peritoneal injury induced by dialysis fluids: is it an option?

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Peritoneal injury induced by dialysis fluids

Peritoneal dialysis (PD) is used to treat end-stage renal disease (ESRD). PD requires the instillation and periodical renovation of PD fluid (PDF) into the peritoneal cavity. PDFs are hyperosmotic solutions generally based on glucose. An osmotic agent is needed to create a gradient that allows a negative fluid balance. However, PDFs may injure the peritoneal membrane in the long term, causing mesothelial cell loss, inflammation, vasodilatation, epithelial–mesenchymal transition (EMT) of mesothelial cells and angiogenesis that lead to fibrosis and ultrafiltration failure. Factors contributing to the bioincompatibility of PDFs include high glucose or glucose degradation product (GDPs) concentrations, low pH and lactate buffer [1]. Bioincompatibility may be reduced by using alternative osmotic agents and glucose-based PDFs with a more physiological pH, lower GDPs concentrations or bicarbonate buffer. Low-GDP PDFs better preserve peritoneal morphology [2, 3]. However, a completely biocompatible PDF will be difficult to achieve, glucose-based PDFs are still needed, and more biocompatible PDFs are expensive so many potential users cannot afford them.

Pharmacological modulation: is it an option?

An alternative approach to preserve the peritoneal membrane, complementary to the efforts aimed at improving PDFs biocompatibility, is the use of pharmacological agents protecting the mesothelium or targeting inflammation and fibrosis. The feasibility of two chronic pharmacological intervention approaches has been tested in experimental PD. One was the addition of pharmacological agents to the PDFs. This approach has been useful for proof-of-concept studies. Industrial addition of therapeutic agents as another component of PDF could be interesting for the future. However, incorporation of new components of PDFs requires major changes from a regulatory point of view and will increase the cost of PD. Self administration of a therapeutic agent into the PDF by the patient will also increase the cost of PD and has a potential risk of PDF contamination. The other approach, the use of oral agents, is technically easier.

The general response to tissue injury involves inflammation to eliminate the insult as well as damaged tissue in order to restore its architecture and functionality. An adequate control of inflammation is essential to avoid scarring. Sustained inflammation promotes fibrosis and angiogenesis, processes associated with the ultrafiltration failure that causes PD technique dropout. PD patients present a chronic inflammatory state and may suffer acute inflammatory processes induced by infection or ‘haemoperitoneum’ [2]. A better understanding of the role and regulation of inflammation in PD-related peritoneal damage is essential to design novel therapeutic strategies to protect the peritoneal membrane.

Experimental approaches

Glucose and GDPs are the key promoters of peritoneal injury and inflammation [1]. High-glucose high-GDP PDFs have been used in experimental models in order to accelerate peritoneal injury. Interventional studies have explored the efficacy of peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists, cyclooxygenase (COX)-2 inhibitors, renin–angiotensin system (RAS) targeting and bone morphogenic protein (BMP)-7 in protecting the peritoneal membrane (Table 1).

Oral PPAR-γ agonists

PPAR-γ agonists, such as rosiglitazone, improve insulin sensitivity and exert immunomodulatory actions on macrophages and T cells [4, 5]. Oral rosiglitazone was tested in mice with chronic peritoneal exposure to high-glucose
high-GDP PDF for 3 weeks. Similar to long-term PD, this model results in loss of mesothelial cells, EMT, inflammation, fibrosis and decreased ultrafiltration [6]. Rosiglitazone reduced peritoneal advance glycation end-product (AGE) accumulation, preserved the mesothelial cell monolayer, reduced fibrosis and angiogenesis and improved peritoneal ultrafiltration. This was associated with increased peritoneal concentration of the anti-inflammatory cytokine interleukin-10 (IL-10) and with a higher percentage of CD4+CD25+FoxP3+ regulatory T cells (Tregs). Tregs secrete IL-10 and regulate Th1, Th2 and Th17 responses.

**COX-2 inhibition**

COX enzymes catalyse prostaglandin (PG) synthesis [7]. Traditional non-steroidal anti-inflammatory drugs, such as ibuprofen, inhibit both COX-1 and COX-2. COX-1 is constitutively expressed in various tissues and has physiological roles. However, expression of COX-2 is regulated by mitogenic and inflammatory stimuli and is related to pathological processes, including inflammation and angiogenesis [7]. COX-2 promoted renal expression of transforming growth factor-β1, fibronectin and vascular endothelial growth factor in a rat model of diabetes and hypertension [8]. High glucose concentrations increase the synthesis of PG-E2 in human peritoneal mesothelial cells [9]. AGEs induce the expression of COX-2 and the secretion of PG-E2 in human peripheral blood monocytes [10]. In mouse or rat PD models, the orally administered COX-2 inhibitor celecoxib decreased peritoneal inflammation, angiogenesis, fibrosis and preserved ultrafiltration [2, 11].

**RAS targeting**

Angiotensin II promotes fibrosis and inflammation in various tissues [12, 13]. RAS inhibition with intraperitoneal or oral enalapril, valsartan or losinopril reduced peritoneal thickening and loss of ultrafiltration induced by 4 weeks of daily hypertonic PDF exposure in rats [14, 15].

**Intraperitoneal BMP-7**

BMP-7 promotes mesenchymal to epithelial transition and prevents and reverses fibrosis *in vitro* and *in vivo* in murine models of renal injury [16, 17]. In rats, BMP-7 added to high-glucose high-GDP PDF for 5 weeks decreased features of mesothelial cell EMT and reduced fibrosis and angiogenesis. However, these effects may be independent from the inflammatory response since BMP-7 did not modulate the influx of activated macrophages to the tissue nor the total number of intraperitoneal cells [18].

### Prospects for clinical approaches

Animal models provide proof-of-concept evidence for the feasibility and potential efficacy of targeting pathways involved in inflammation and fibrosis in order to preserve the peritoneal membrane. Is there a potential clinical application for agents studied in these models? The clinical use of some of the specific compounds tested so far in animals may encounter several hurdles. Thus, side effects associated with thiazolidinediones include oedema, weight gain, bone fracture risk, heart failure and an adverse lipid profile [19]. This has led to the recent withdrawal from the European market of rosiglitazone [20]. Prolonged use of COX-2 inhibitors may exert vasoconstrictor and thrombogenic effects [21], especially worrisome in ESRD patients, who have a high cardiovascular risk [22]. The use of BMP-7 may be associated with ossification; indeed, BMP-7 has been administered locally into bone lesions to promote bone formation [23]. Immunomodulatory drugs may have an impact on the risk or severity of peritonitis. Thus, PPARγ activation may enhance anti-fungal responses [24]. Further studies are needed in this regard since none of the *in vivo* PD studies addressed infectious complications. Still, independently of any specific drug considerations, pre-clinical studies support the feasibility of modulating pharmacologically the peritoneal response to bioincompatible PDs.

Clinical trials on pharmacological intervention to preserve peritoneal integrity or function have been performed or are underway. Heparin has anticoagulant activity, modulates extracellular matrix synthesis, cellular proliferation, angiogenesis and inflammation and is incorporated into the peritoneal membrane when administered intraperitoneally with PDF to rats [25]. Intraperitoneal tinzaparin, a low-molecular-weight heparin, reduced peritoneal permeability to small solutes and increase ultrafiltration in PD patients [26]. A Phase II trial addressed the modulation of ultrafiltration by bemiparin in icodextrin (3500 IU per bag) PDF in 76 patients with low ultrafiltration capacity and/or high peritoneal creatinine transport. These results were recently presented in abstract form (XIeme Symposium RDPLF, 14 April 2011). By intention-to-treat analysis, ultrafiltration capacity was not different at 8–16 weeks. However, in patients with ultrafiltration failure, there was a clinically significant increase in ultrafiltration under bemiparin. No increases in

<table>
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<th>Treatment</th>
<th>Inflammation</th>
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<th>Fibrosis</th>
<th>Angiogenesis</th>
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*ND, no data.*

**Table 1. Potential pharmacological intervention to preserve the peritoneal membrane in PD**
peritonitis rate or major bleedings were observed, but bemi-parin was absorbed from the peritoneum in some patients. The effects of rosiglitazone on inflammation, vascular injury and survival in PD patients are under study [27]. Some drugs routinely administered to patients with ESRD may also protect the peritoneal membrane. Thus, RAS blockade is common in PD patients and preserves renal function. In rat models, it protects from peritoneal thickening and ultrafiltration and vascular alterations [14, 28, 29]. An ongoing study is exploring the effect of enalapril and losartan on peritoneal inflammation and vascular alterations [14, 28, 29]. An ongoing study in rat models, it protects from peritoneal thickening and ultrafiltration and vascular proliferation in rat PD [31, 32]. Activators of vitamin D receptor (VDR) are used to treat secondary hyperparathyroidism in PD patients. VDR activation modulates inflammation, fibrosis and immune responses, modifying the Th1/Th2 pattern, inducing Tregs and decreasing nuclear factor κ B activation [33]. It also exerts anti-proliferative actions, increases anti-fibrotic factors such as BMP-7 and metalloproteinase-8 and decreases renal fibrosis [33]. However, the potential benefit of VDR activators for the peritoneum has not been studied yet.

Take-home message

Pharmacological interventions targeting inflammation and EMT represent interesting approaches to limit peritoneal damage during PD. Careful benefit/risk studies are required. Ideally, we should better understand the potential benefits for the peritoneum of drugs that may serve multiple purposes for PD patients. Since a key market for these approaches is the low income countries that cannot afford the newer, more biocompatible PDFs, cost will be an issue and generic drugs are preferable over new compounds. In one scenario, patients may use the drug for as long as they are on PD. In other scenarios, the drugs would be required during especially vulnerable periods, as the peri-peritonitis period or when hyperosmotic PDF are needed. Since experimental studies have only addressed protection from high-GDP PDFs, the potential benefits of any such approaches on low-GDP PDFs are unclear.

References


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Are the high mortality rates in dialysis patients mainly due to cardiovascular causes?

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It is a well-known fact that chronic dialysis patients have a markedly increased mortality compared to the general population. In a recently published analysis of the European Renal Association–European Dialysis and Transplant Association Registry, the mortality rate in incident dialysis patients was 192 per 1000 person-years, while it was only 12.05 in the general population [1]. Despite the emphasis on the importance of accelerated atherosclerosis and cardiovascular death in dialysis patients [2], the excess mortality in them was due to both cardiovascular (39%) and non-cardiovascular (51%) causes. The distribution of the causes of death was not different from that in the general population. The standardized mortality ratio for cardiovascular death was 42.9 in dialysis patients compared to 4.9 in the general population. For non-cardiovascular death, these figures were 57.1 and 7.0. This ‘normal’ distribution of mortality causes may lead to a different view on risk factors for mortality in dialysis patients. Also, factors that have been linked to cardiovascular death are often associated with non-cardiovascular mortality. This has been found for C-reactive protein [3], fetuin A [4] and possibly troponin T [5], making it likely that death from various causes is often associated with the presence of an acute-phase reaction.

Causes of non-cardiovascular causes of death

Infections and malignancies are the most common causes of non-cardiovascular death [1]. Septicaemia and pneumonia are the most common infections in dialysis patients associated with death [6–8]. The presence of a non-native vascular access device, including a central venous catheter, is the most important cause for septicaemia or bacteraemia leading to death in haemodialysis (HD) patients [6]. The hazard ratio for peritoneal dialysis (PD) patients was not different from that in HD patients with an arteriovenous fistula.

Pneumonia is the other serious infection in dialysis patients. The adjusted hazard ratio for death was 5 in an analysis of the Medicare database in the USA [8]. In multivariate analysis, not only the presence of chronic obstructive pulmonary disease but also HD as initial treatment was associated with a higher chance of getting pneumonia compared to PD. The lower incidence of septicaemia in PD patients compared to HD is not unexpected, the lower