ABSTRACT

Acute and chronic reactive peritonitis in peritoneal dialysis: neurogenic inflammation and citrate treatment

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The prevalent problems associated with peritoneal dialysis (PD) are ultrafiltration failure and peritonitis. During PD the patient is sustained on a state of intraperitoneal inflammation, which over time impairs structure, and function of the peritoneal membrane, leading to loss of ultrafiltration efficacy. The aims of this project was: to establish whether neurogenic inflammation and mast cell activation are triggered by PD fluid exposure and to evaluate the effects of citrate as an additive to PD fluid in acute and chronic animal models.

The studies were conducted in rats, exposed to filter sterilised lactate or lactate/citrate buffered PD fluid with glucose (2.5 and 3.9 %) as osmotic agent through an implanted catheter. Acute studies were based on single exposure and long-term studies on daily exposures for a period of 5 weeks. Pharmacological intervention was used to study mast cell activation and the neurogenic inflammatory response.

Histamine was released into the peritoneal cavity within 30 minutes of infusion of standard PD fluid. Also osmotically neutral fluid triggered a histamine release from mast cells. Indirect evidence for the release of neuropeptides SP and CGRP suggested actions of a neurogenic inflammation. Mast cell activation was shown to be dependent on substance P stimulation of its receptor, NK-1. Inhibiting NK-1 significantly reduced vascular albumin loss from the blood to the peritoneal cavity by a mast cell independent mechanism. Blocking CGRP resulted in a significant increase in osmotic and net ultrafiltration. The classic trigger of neuropeptide release, the TRPV1 receptor was, unexpectedly, not responsible for neuropeptide actions in the present model.

Substituting 5-15 mM lactate with equal amounts of citrate gradually improved osmotic ultrafiltration (fluid transport) compared with lactate PD fluid, suggesting a dose-response relationship. Significantly improved net ultrafiltration (fluid gain) was the result of increased osmotic ultrafiltration, in response to 10 - 15 mM citrate substitution.

Long-term treatment with citrate-substituted PD fluid in rats did not significantly reduce fibrosis and angiogenesis of the peritoneal membrane compared with standard PD fluid. PD catheter patency was, however, significantly improved in animals treated with citrate substituted PD fluid. Macroscopic signs of fibrosis were also significantly reduced by citrate.

The clinical implications are that pharmacological intervention with the neurogenic inflammatory response and calcium chelation with citrate have potential to improve the efficiency of peritoneal dialysis.

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I. **Cavallini N, Wieslander A, Braide M.**
Substituting citrate for lactate in peritoneal dialysis fluid improves ultrafiltration in rats. *Perit Dial Int*. 2009 Jan-Feb; 29(1): 36-43.

II. **Cavallini N, Delbro D, Tobin G, Braide M.**
Neuropeptide release in response to PD exaggerates serum albumin loss and reduces ultrafiltration. (2009) M*anuscript*

III. **Cavallini N, Braide M.**
Fibrosis, angiogenesis and catheter patency in 5 weeks citrate PD in rats. (2009); submitted to *Perit Dial Int*

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