Rat models in peritoneal dialysis

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Abstract

Background. It is widely accepted that the currently used dialysis solutions are not biocompatible with the peritoneal membrane. Therefore, animal studies have been performed to study different aspects of peritoneal dialysis. However, representative models mimicking the human situation are not yet available.

Methods. The effect of a single injection of peritoneal dialysis (PD) fluid on the cellular composition was studied. Thereafter, the effect of a single injection of PD fluid on bacterial clearing was tested over time. Finally, an in vivo rat model was established to study the effects of long-term exposure to PD fluid on the peritoneal membrane and the local host defence (peritoneal cells).

Results. In the rat model, long-term daily exposure is possible. The ‘drop-out’ after 9–10 weeks on the most commonly used PD fluid Dianenal 3.86%, however, is ~50% due to omental wrapping. In the remaining study group, large differences were observed (as compared with controls), especially with respect to morphological parameters.

Conclusions. The rat peritoneal continuous exposure model seems to have potential for intervention studies, since it uses no additions, no antibiotics and no omentectomy, and gives continuous long-term exposure to PD fluid. However, problems still remain: ‘drop-out’ is quite often seen and this non-uraemic exposure model does not totally mimic the situation present in continuous ambulatory PD patients.

Keywords: CAPD; PD models; peritoneal dialysis fluids; rat

Introduction

It is now well accepted that the currently used dialysis solutions are not biocompatible with the peritoneal membrane [1]. The development of new and more physiological peritoneal dialysis (PD) solutions is therefore one of the major research focuses (for a review, see [2]). In order to test more biocompatible fluids, there is a need for in vivo animal models for preclinical evaluation [3]; this eventually should include a proper uraemic model [4,5]. Here we discuss past and present studies in rat PD models from our group, especially with respect to the potential and problems, relevant to clinical PD.

Results and discussion

Previously, we showed [6] that a single acute administration of 10 ml of PD fluid into the peritoneal cavity of the rat induced an acute inflammatory state, in comparison with the minor effects observed after saline infusion. The effect of prior injection of PD fluid on in vivo bacterial clearing showed that glucose concentration in the PD fluid impaired the antibacterial host defence. Moreover, the effect of the dwell time (time between PD fluid administration and bacterial infection) was also important (negative correlation with dwell time) [7].

To study the long-term effect of dialysis fluids on the peritoneal cell layers and the local defence mechanism, an in vivo rat model was developed [8]. Mini vascular access ports were implanted subcutaneously in the neck of rats, and an attached catheter was tunnelled subcutaneously towards the abdomen and inserted into the peritoneal cavity. This model allows the assessment of not only immune parameters [8], but also the morphological–functional relationship [9] after long-term exposure (up to 20 weeks) to various dialysis solutions.

The potential of this model is obvious. No omentectomy was performed; therefore, the morphological changes in the state of this important immunological organ [10] can also be analysed. As can been seen in
Figure 1, there is a strong increase in both the number and size of the milky spots.

Moreover, with this approach, the peritoneum is exposed long term to the PD fluid, since ~18 h [5] are needed for the fluid to be absorbed, and every 24 h new PD fluid is administered. No antibiotics, heparin or further additions were given.

Some problems still remain. (i) As seen in Figure 2 in three separate experiments (A, n=14; B, n=15; C, n=16), after 9–10 weeks of daily peritoneal exposure to the most commonly used PD fluid, Dianeeal 3.86%, there is a 'drop-out' of ~50% of the animals (40–60% in the three different experiments). (ii) This 'drop-out' is due mostly to omental wrapping (Figure 3) around the tip of the catheter, which made it impossible to continue the daily injection of PD fluid in these animals. Zweers et al. [9] noted a much lower 'drop-out', but in their approach heparin was added to the PD fluid. (iii) The animals were not uraemic, unlike those described by Lameire et al. [5]. However, in their studies, a large number of animals died before long-term studies could be completed. The combination of a uraemic model [5] with the developed chronic exposure model [8] would be an attractive alternative and presently is being studied. (iv) The daily exposure model unfortunately does not allow collection of effluent.

Finally, with the potential and problems in mind, it has been possible to compare the effects of some PD fluids in vivo on various parameters in our model (bacterial clearing, see Hekking et al. [8]; morphology of the peritoneum, see Zweers et al. [9]). Beside the data given in this present overview (especially focused on the 'drop-out' and the changes in the omentum), these studies have shown that relevant changes with respect to fibrosis, neo-vascularization, bacterial killing and peritoneal permeability characteristics can be obtained. Future studies will investigate the exact differences between different PD fluids and in particular will unravel the role of pH, glucose and glucose degradation products in the induction of these changes.

We conclude that, within given limitations, this exposure model is suitable for studying some effects relevant to the clinical PD setting and offers the possibility for future intervention studies.

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References