A Spatially Distributed Approach of Intraperitoneal Fluid Kinetics Combined With Its Transport through the Interstitium during Peritoneal Dialysis

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In intraperitoneal therapies, fluid infusion to peritoneal cavity is used to treat patients with impaired kidney function or those requiring resuscitation due to ischemia or for regional treatment of intraperitoneal cancer. During peritoneal dialysis, infusion of a hypertonic (typically glucose based) solution into the peritoneal cavity results in bidirectional fluid and solute flow between dialysate and blood flowing through the underlying tissue. All these processes occur on different spatial scales as abdominal organs (with different transport characteristics), blood and lymph capillary beds, cells, interstitium, capillary wall pores, and water channels (transcellular proteins called aquaporins) in cellular membrane. There are also time scale differences as in a short term (minutes or hours, for example, vasodilation due to hypertonicity of the peritoneal dialysis fluid) and long term (days, for example changes in the tissue homeostasis due to frequent fluid exchanges, months, as protein glycation, epithelial - mesenchymal transition, tissue fibrosis and angiogenesis).

Typically phenomenological models (such as membrane model, three pore model) are used in clinical and experimental practice to characterize transport properties of the "peritoneal membrane" and therefore efficiency of the treatment. The main advantage of the compartmental approach is that it substantially decreases the number of parameters that need to be estimated, and therefore its application in clinical research is easier. However, in the compartmental approach, it is usually difficult to connect derived parameters with the physiology and the local anatomy of the involved tissues. Therefore, these models are not well suited to describe the transient processes changes that occur as part of the modeled phenomena. The goal of this study was to propose mathematical model derived from the local physiology, and tissue structure, that would describe fluid kinetics in peritoneal cavity.

The standard distributed model integrates the transport processes at different levels: 1) the multiorgan level (dialysis fluid bathes all organs in the peritoneal cavity), 2) tissue level with separated pathways for fluid and solute exchange (interstitium, cells, capillary wall, lymphatics), and 3) microscale with pores in interendothelial clefts and aquaporins in endothelial cells. The model describes fluid and solute transport in the tissue perpendicular to the surface across uniform interstitium using partial differential equations for fluid transport driven by osmotic and hydrostatic pressures (extended Darcy law) and solute transport due to diffusion and convection. Capillary and lymphatic beds are described as continuously distributed within the tissue layer that surrounds the peritoneal cavity and allow for the exchange of fluid and solutes between blood and the tissue. The capillary wall is simulated with three types of pores: large pores that allow the leakage of proteins from blood to interstitium, small pores for the exchange of fluid and small solutes, and ultrasmall pores (aquaporins) for exclusive water transport. The interstitium is considered as an expandable structure that can increase its fluid void volume fraction if the interstitial hydrostatic pressure is increased. Tissue local parameters are assumed dependent on the interstitial hydration and vasodilatation induced by glucose is taken into account. The changes of intraperitoneal volume and solute concentrations in dialysate (after fluid infusion) depend on the fluid and solute absorption from the peritoneal cavity and local net fluid and solute flow from the tissue. In addition, fluid and solute flow from the peritoneal cavity into the tissue layer that surround peritoneal cavity, has impact on tissue hydration and interstitial solute concentrations. In the model, the intraperitoneal kinetics of volume and solute is described by the system of ordinary differential equations, which are coupled with the system of partial differential

equations that describe transport through the tissue. Transport of water and small solutes, such as glucose, urea, creatinine and sodium, has been considered.

The model has been implemented in Matlab. Numerical procedures were written in order to couple, partial and ordinary differential equations. Moreover, additional procedures have been proposed to allow for quick fitting of the model to the clinical data, and fast generation of different scenarios based on the obtained parameters. The model was fitted to the average volume and solute concentrations profiles from dwell studies of clinically stable CAPD patients using typical glucose based solutions: 1.36%, 2.27% or 3.86% of glucose. Daily consecutive fluid exchanges has been modeled and simulated taking into account 10 minutes of fluid infusion, dwell time, and 10 minutes of draining procedure. The dependence of effective peritoneal surface area on the intraperitoneal volume was assumed based on clinical studies. Because there is no available clinical data on the changes that occur in the tissue during clinical PD, the predicted profiles of hydrostatic pressure and solute concentration in the tissue were validated on the basis of animal experiments.

Implemented numerical procedures, which were designed particularly for the model, allows us to obtain full simulation of a 6h fluid exchange in about 10 to 30 seconds on a standard desktop PC. In order to validate model, fitting procedure has been apply to the clinical data for three different glucose based dialysis fluids. The model was able to describe the clinical data with high accuracy, as presented on Figure 1. The weighted least squares error of the model adjustment does not exceed 0.043.

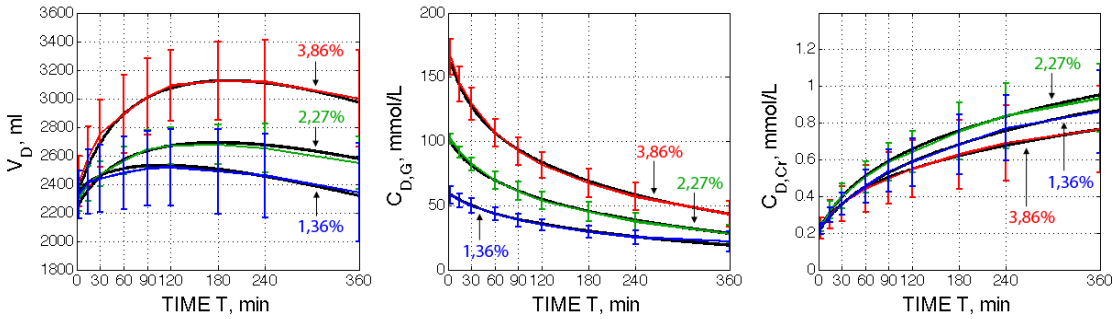

Figure 1. Comparison between clinical data and model results for fluid solute kinetic in peritoneal cavity. The figures represent (starting from the left, upper figure) intraperitoneal volume (V_D), and concentration of glucose ($C_{D,G}$), and creatinine ($C_{D,Cr}$) in dialysate, as a function of dwell time, respectively. The mean +/- SD values from dwell studies of patients for different glucose based dialysis fluid are denoted as follows: red line – glucose 3.86%, green line – glucose 2.27%, blue line – glucose 1.36%, whereas model results are denoted by black line.

In addition to the description of kinetic in dialysate, model permits the evaluation of tissue alterations during peritoneal dialysis and their relationship to the changes in intraperitoneal dialysis fluid, c.f. Figure 2. Numerical simulations of the models suggest increase tissue hydration and glucose concentration close to the peritoneal cavity, c.f. Figure 2. A transient negative hydrostatic pressure of interstitial fluid (indicating local tissue dehydration) was observed in the computer simulations during the initial phase of the peritoneal dwell. Urea and creatinine in the tissue tended to equilibrate with the respective levels in dialysate and therefore their concentrations close to the peritoneal surface decreased rapidly. However, constant inflow of urea and creatinine from blood to the tissue, as well as the increasing levels of their concentrations in peritoneal cavity, allow for the increase of their concentrations close to the peritoneal surface (Figure 2). Nevertheless, their concentrations at the end of a dwell remain lower than their physiological levels within the distance 0.2 cm from the peritoneal cavity.

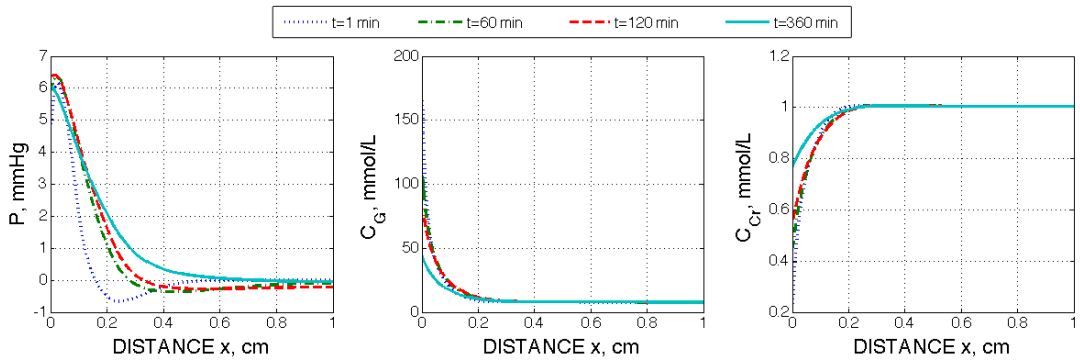

Figure 2. (In the order from the left figure) Interstitial hydrostatic pressure (P), and interstitial concentrations of glucose (C_G), and creatinine (C_{Cr}), as a function of distance from the peritoneal cavity, x, at dwell time t=1, 60, 120, and 360 minutes in the case of dialysis fluid glucose 3.86%.

Computer simulations of 4 consecutive fluid exchanges suggest significant differences between first dialysis and consecutive dwells. Residual fluid that remains in the peritoneal cavity together with the perturbed (after first exchange) tissue hydration and interstitial solute concentrations, result in the observed changes in the tissue profiles as well as kinetics of dialysate in the next exchanges, Figure 3. Numerical simulations suggest that after first day of peritoneal dialysis only minor changes in the interstitial and intraperitoneal are observed.

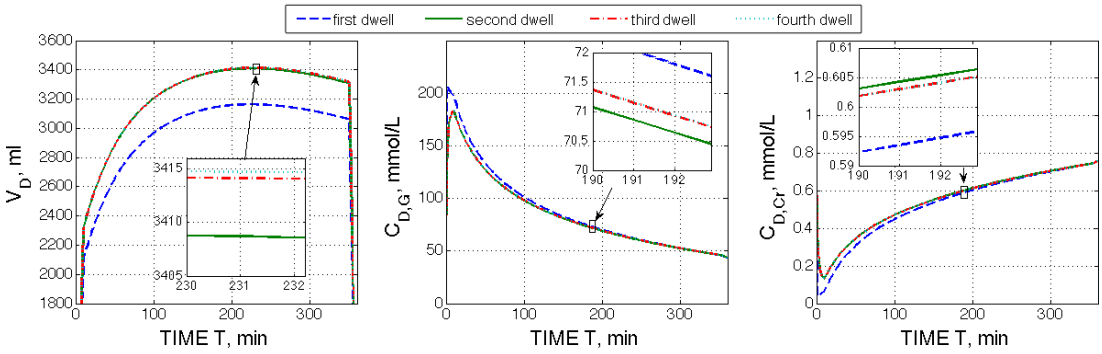

Figure 3. The intraperitoneal volume (V_D), and intraperitoneal concentrations of glucose ($C_{D,G}$) and creatinine ($C_{D,Cr}$) as a function of dwell time for 4 consecutive fluid exchanges with glucose 3.86% during first day of peritoneal dialysis. The fluid exchange procedure takes into account 10 minutes of fluid infusion, 6 hour dwell time, and 10 minutes of drainage, the residual volume of 200 mL is assumed.

The model provides the link between kinetic of dialysis fluid that can be measured in clinical and experimental studies and the corresponding changes in the tissue, during single dwell and consecutive fluid exchanges. It can be used for a prediction of the alteration of tissue hydration and interstitial solute concentration during hypothetical consecutive fluid exchanges. This also opens pathways to more detailed physiological interpretation of the transport parameters measured in clinical and experimental studies.