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Optimizing Automated Peritoneal Dialysis Using an Extended 3-Pore Model

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Introduction: In the current study, an extended 3-pore model (TPM) is presented and applied to the problem of optimizing automated peritoneal dialysis (APD) with regard to osmotic water transport (UF), small/middle-molecule clearance, and glucose absorption.

Methods: Simulations were performed for either intermittent APD (IPD) or tidal APD (TPD). IPD was simulated for fill and drain volumes of 2 L, whereas TPD was simulated using a tidal volume of 0.5 L, 1 L, or 1.5 L with full drains and subsequent fills (2 L) occurring after every fifth dwell. A total of 25 cycles for a large number of different dialysate flow rates (DFR) were simulated using 3 different glucose concentrations (1.36%, 2.27%, and 3.86%) and 3 different peritoneal transport types: slow (peritoneal equilibrium test $D/P_{crea} < 0.6$), fast (peritoneal equilibrium test $D/P_{crea} > 0.8$), and average. Solute clearance and UF were simulated to occur during the entire dwell, including both fill and drain periods.

Results: It is demonstrated that DFRs exceeding ~ 3 L/h are of little benefit both for UF and small-solute transport, whereas middle-molecule clearance is enhanced at higher DFRs. The simulations predict that large reductions (> 20%) in glucose absorption are possible by using moderately higher DFRs than a standard 6 × 2 L prescription and by using shorter optimized "bi-modal" APD regimens that alternate between a glucose-free solution and a glucose-containing solution.

Discussion: Reductions in glucose absorption appear to be significant with the proposed regimens for APD; however, further research is needed to assess the feasibility and safety of these regimens.

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Autumated peritoneal dialysis (APD) is peritoneal dialysis performed with the aid of a mechanical device (a cycler), freeing the patient or caregiver from the repetitive labor of replacing spent dialysis fluid manually. APD is usually performed during the night when the patient is asleep, followed by a "dry day" or a single long daytime dwell ("wet day"). Compared to conventional techniques, such as continuous ambulatory peritoneal dialysis, APD offers the possibility to use increased dialysate flow rates (DFRs), which would be either impractical or impossible to accomplish manually. Increasing the DFR by using more frequent exchanges will typically improve the efficiency of APD.[1] However, an increased DFR will increase the time spent filling and draining the peritoneal cavity, reducing the efficiency of the dialysis at higher DFRs.[2,3] Thus, too frequent exchanges will reduce the efficiency of the dialysis and lead to a reduced cost-efficiency due to the increased consumption of dialysis fluid.

There are 3 exchange techniques of peritoneal dialysis: intermittent peritoneal dialysis (IPD), tidal peritoneal dialysis (TPD), and continuous peritoneal dialysis (CPD).[4] CPD requires the use of dual catheters and has only rarely been used. In IPD, each dwell is followed by a complete drain, after which the peritoneal cavity is filled again with fresh dialysate. The outflow of drained fluid is biphasic, having a "fast phase" with flows ~ 350 ml/min, and a "slow phase" with significantly lower flows, being only 30 to 40 ml/min.[5,6] The separation between the fast and slow outflow phase is called the transition or break point, which usually occurs after ~ 5 minutes after a 2-L dwell.[4] In TPD, after an initial fill volume (of usually 2 L), only a portion of the initial fill volume is drained and replaced by fresh dialysis fluid during each cycle. Thus, there is always a certain minimal amount of dialysate that stays in contact with the peritoneal membrane throughout the dialysis session, after

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which the peritoneal cavity is drained completely. A prescription of TPD is usually defined by the percentage of the initial fill volume delivered to the patient during subsequent dwells after the initial dwell. For example, 50% TPD for a 2-L initial fill volume means that the cycler is programmed to deliver 1 L of tidal fill volume (TFV) at the start of each dwell subsequent to the initial dwell. In addition to draining the TFV, cyclers usually allow the prescriber to drain a surplus amount of fluid to compensate for the expected ultrafiltration (UF) to avoid overfilling the peritoneal cavity with the accumulated ultrafiltrated volume. Thus, the tidal drain volume is usually larger than the TFV. However, in clinical practice, it is difficult to exactly match the predicted UF with the actual UF, and thus a certain amount of "overdrain" or overfill is unavoidable.

The TPM was originally derived directly from patient data, some of which were published in 1990,[7] focusing on the most difficult task of peritoneal dialysis (PD) modeling, namely, to model UF volume as a function of time. The first head-to-head comparison of the TPM in its original version versus conventional models (the Pyle and Popovich model) was done by Vonesh and Rippe,[8] fitting the 2 fundamentally different models to rather detailed patient data. It was shown that the 2 models' ability to predict UF volume curves for 360 minutes were identical. The Pyle and Popovich model operated with high reflection coefficients to small solutes. It also used an albumin oncotic pressure term, contributing to the total fluid loss from the peritoneal cavity, whereby the lymph flow (parameter) became 0.54 ml/min in the Pyle and Popovich model (compared to 0.3 ml/min in the TPM). Although mathematical predictability was excellent, using non-TPM reflection coefficients and an inflated lymph flow parameter, problems with the Pyle and Popovich model turned up when simulating drained volume-versus-time curves for icodextrin. Furthermore, in dwells lasting $>$ 6 hours, the rate of final reabsorption became too large. This was the reason why the Pyle and Popovich model was abandoned for the purpose of UF simulations in favor of the TPM in Vonesh's later models (cf. PD-Adequest).[9] A modified version of the TPM has been extensively validated by Haraldsson in 1995,[10] and later by its use in the computer software PDC. The Haraldsson modification of the TPM included an initial inflation parameter for small-solute permeability–surface area product (PS) values, essentially operating during the first hour of the dwell. Because PS to glucose was not inflated during the entire dwell, the term "final reabsorption rate" had to be increased from $\sim$ 1.1 to $\sim$ 1.5 ml/min to fit measured UF data.[7,8] The TPM is thus very well validated, and is especially suitable for modeling of icodextrin[15] and long (>6 hours) dwells, which is problematic with most other models.

The classic TPM does not describe the inflow or outflow phase of the dwell. However, at higher dialysate flows, a significant part of the exchange time is spent either filling or draining the peritoneal cavity. In the current study, we present an extended TPM with an additional compartment that allows simulation also of the drain and fill phases of the dwell. The extended model is used to optimize the treatment with APD with regard to osmotic water transport (UF), small/middle-molecule clearance, and glucose absorption. The results demonstrate that the "metabolic cost" in terms of glucose absorption can be significantly reduced ($>$ 20%) by using slightly higher DFRs than usually prescribed and a "bimodal" regimen in which relatively short dwells containing a high glucose concentration are combined with longer dwells containing no or a low glucose concentration. In addition, it is demonstrated that these regimens make it possible to shorten the total treatment time while achieving the same or better small-solute transport and UF.

MATERIALS AND METHODS

During peritoneal dialysis, the net volume flow across the peritoneal membrane, at any time t from the start of the filling phase, is assumed to be the sum of 6 different volume flows

$$\frac{dV_D}{dt} = J_{v,C} + J_{v,S} + J_{v,L} - L + J_{fill} - J_{drain} \qquad (1)$$

In this equation, $J_{v,C}$, $J_{v,S}$, and $J_{v,L}$ represent the net flow of water (in ml/min) across the aquaporines, the highly selective pathways ("small pores") and the weakly selective pathways ("large pores"), respectively. In the TPM, the flows in equation 1 are assumed to vary only as a function of time and are directed into the peritoneal cavity when positive. The net lymphatic clearance from the peritoneal cavity to the circulation is denoted L (in ml/min) and is typically on the order of 0.2 to 0.3 ml/min when measured as a clearance to the circulation.[11] The clearance of an i.p. volume marker is typically larger than this value, which has been the source of much discussion.[12,13] The model in the present work has been extended to include also the fill and drain phases of the dwell. J_{drain} and J_{fill} represent the flows of volume (in ml/min) to and from the source of dialysis fluid, respectively. The change in the i.p. concentration for each solute i (denoted $dC_{D,i}/dt$ in