

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 $D/P_{\text{crea}} < 0.6$), fast (peritoneal equilibrium test $D/P_{\text{crea}} > 0.8$), 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.

Kidney Int Rep (2017) 2, 943–951; <http://dx.doi.org/10.1016/j.ekir.2017.04.010>

KEYWORDS: automated peritoneal dialysis; dialysis efficiency; PD prescription; 3-pore model; urea kinetics

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Automated peritoneal dialysis (APD) is peritoneal dialysis performed with the aid of a mechanical device (a cyclor), 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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²Deceased 20 October 2016.

Received 31 December 2016; revised 4 March 2017; accepted 21 April 2017; published online 27 April 2017

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 cyclor 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, cyclors 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 ~ 1.1 to ~ 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 icodextrin¹⁵ 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

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

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

mmol/ml/min) at any time t is dependent on 3 separate terms

$$\frac{dC_{D,i}}{dt} = \frac{J_{s,S,i} + J_{s,L,i}}{V_D} - C_{D,i} \frac{J_{v,C} + J_{v,S} + J_{v,L} + J_{fill}}{V_D} + \frac{C_{B,i} J_{fill}}{V_D} \quad (2)$$

The first term is the change in i.p. concentration caused by the flow of solutes (through small and large pores, $J_{s,S,i}$ and $J_{s,L,i}$ in mmol/min) in and out of the peritoneal cavity. As can be seen, a positive solute flow is directed into the peritoneal cavity, increasing the concentration in the dialysate. The second term represents the dilution/concentration due to volume flux in and out of the peritoneum. The last term is the change in concentration due to the inflow of dialysate J_{fill} having a concentration $C_{B,i}$ (in mmol/ml). The change in concentration in the drain reservoir of solute i ($dC_{B,i}(t)/dt$ in mmol/ml/min) is given by

$$\frac{dC_{B,i}}{dt} = \frac{J_{drain} C_{D,i} - J_{fill} C_{B,i}}{V_B} - \frac{C_{B,i}}{V_B} \frac{dV_B}{dt} \quad (3)$$

The change in reservoir volume V_B is simply

$$\frac{dV_B}{dt} = -J_{fill} + J_{drain} \quad (4)$$

Thus, the concentration in the reservoir does not change during the fill phase ($dC_{B,i}/dt = 0$). This equation implies that the drain compartment is identical to the compartment with fresh dialysis fluid, which is not the case in actual practice. However, because drain fluid and fresh dialysate are never mixed, there is no need for more than 1 “reservoir” compartment in the model. Hence, the compartment V_B acts as a source during the fill phase and as a collector of drain fluid during the drain phase. The initial conditions are

$$V_D(0) = V_r \quad (5)$$

$$C_{D,i}(0) = C_{P,i} \quad (6)$$

$$C_{B,i}(0) = C_{I,i} \quad (7)$$

$$V_B(0) = V_I \quad (8)$$

where V_r is the residual volume, V_I the fill volume (or 0 at the start of the drain phase), $C_{I,i}$ is the dialysis fluid concentration, and $C_{P,i}$ is the plasma concentration of solute i , which is assumed to be constant during the dwell. The ordinary differential equations 1 to 4 above, along with the initial conditions, was solved with a fourth-order Runge-Kutta scheme (see Detailed Methods in Supplementary Material) to obtain the functions $V_D(t)$, $C_{D,i}(t)$, $V_B(t)$, and $C_{B,i}(t)$. A glossary of terms can be found in Supplementary Table S1.

Volume and Solute Flow in the TPM

The solute flow (in mmol/min) over each pathway is calculated according to the Patlak equation

$$J_{s,S,i} = J_{v,S} (1 - \sigma_{S,i}) \frac{C_{P,i} - C_{D,i} e^{-Pe_{S,i}}}{1 - e^{-Pe_{S,i}}} \quad (8)$$

$$J_{s,L,i} = J_{v,L} (1 - \sigma_{L,i}) \frac{C_{P,i} - C_{D,i} e^{-Pe_{L,i}}}{1 - e^{-Pe_{L,i}}} \quad (9)$$

where $Pe_{S,i} = J_{v,S}(1 - \sigma_{S,i})/PS_{S,i}$ and $Pe_{L,i} = J_{v,L}(1 - \sigma_{L,i})/PS_{L,i}$ are the Péclet numbers (the ratio between the maximum convective and diffusive clearance for solute i) for the small- and large-pore pathway, respectively. The mass transfer area coefficients, $PS_{S,i}$ and $PS_{L,i}$ (in ml/min), are either set according to Table 1 or calculated according to pore theory $PS = D \cdot A_0 / \Delta x \cdot A / A_0$, where A/A_0 is the diffusive restriction factor (see also Öberg and Rippe¹⁴) and D is the free diffusion coefficient. The reflection coefficients are calculated according to theory.¹⁵ The volume flow (ml/min) is calculated using Starling equilibria

$$J_{v,C} = \alpha_C L_p S \left(\Delta P - RT \sum_{i=1}^N \varphi_i (C_{P,i} - C_{D,i}) \right) \quad (10)$$

Table 1. Three-pore model parameters

Parameters used for computer simulations of automated peritoneal dialysis according to an extended 3-pore model

Small pore radius (r_s) (Å)	43
Large pore radius (r_l) (Å)	250
Fractional small pore UF coefficient (α_s)	0.900
Fractional transcellular UF coefficient (α_c)	0.020
Fractional large pore UF coefficient (α_l)	0.080
UF coefficient ($L_p S$) (ml/min/mm Hg)	0.074
Osmotic conductance to glucose ($L_p S \sigma_g$) (μl/min/mm Hg)	3.6
Unrestricted pore area over unit diffusion distance for small pores ($A_0/\Delta X$) _s (cm)	25,000 ^a
PS ^b for glucose (ml/min)	15.4 ^c
PS ^b for urea (ml/min)	26.0
PS ^b for Na ⁺ and anions (ml/min)	4.5
PS ^b for phosphate (ml/min)	10.2
Peritoneal lymph flow (L) (ml/min)	0.3
Transperitoneal oncotic pressure gradient ($\Delta\pi_{prot}$) (mm Hg)	22
Peritoneal residual volume (V_r) (ml)	250
Plasma urea concentration (mmol/l)	20
Plasma creatinine concentration (μmol/l)	660
Dialysis fluid sodium concentration (mmol/l)	132
Plasma sodium (and sodium-associated anion concentration) (mmol/l)	140
Plasma glucose concentration (mmol/L)	6.5
Osmotic coefficient for Na ⁺ and anions	0.93

PS, permeability–surface area product; UF, ultrafiltration.

^aWe used 25,000 cm for an average peritoneal transport type, 40,000 cm for high transporters, and 15,000 cm for low transporters.

^bFor average transporters, otherwise scaled according to $A_0/\Delta x$.

^c9.3 ml/min for the disappearance from the dialysate.

$$J_{v,S} = \alpha_S L_p S \left(\Delta P - RT \sum_{i=1}^N \varphi_i \sigma_{S,i} (C_{P,i} - C_{D,i}) \right) \quad (11)$$

$$J_{v,L} = \alpha_L L_p S \left(\Delta P - RT \sum_{i=1}^N \varphi_i \sigma_{L,i} (C_{P,i} - C_{D,i}) \right) \quad (12)$$

where α_C , α_S and α_L are fractional hydraulic conductances for the different pathways (Table 1), φ_i is the osmotic coefficient of solute i , R is the gas constant, and T is the body temperature (310°K). Thus, reflection coefficients are assumed to be the same for osmosis and solute transport (cf. also Deen¹⁶ and Katz *et al.*¹⁷). To account for the recruitment/loss of peritoneal surface area due to a high/low intraperitoneal volume, an area factor was multiplied to all PS values and $L_p S$ according to Keshavia *et al.*¹⁸

$$af = 16.18 \left(1 - e^{-0.00077 \cdot V_D(t)} \right) / 13.3187 \quad (13)$$

Thus, the mass transfer area coefficients and the filtration coefficient were inflated for volumes > 2250 ml and vice versa.

RESULTS

Urea Clearance

In Figure 1, the simulated urea clearance as a function of DFR is plotted for the different techniques (IPD, TPD75/50/25) and different transport types: fast (red line)

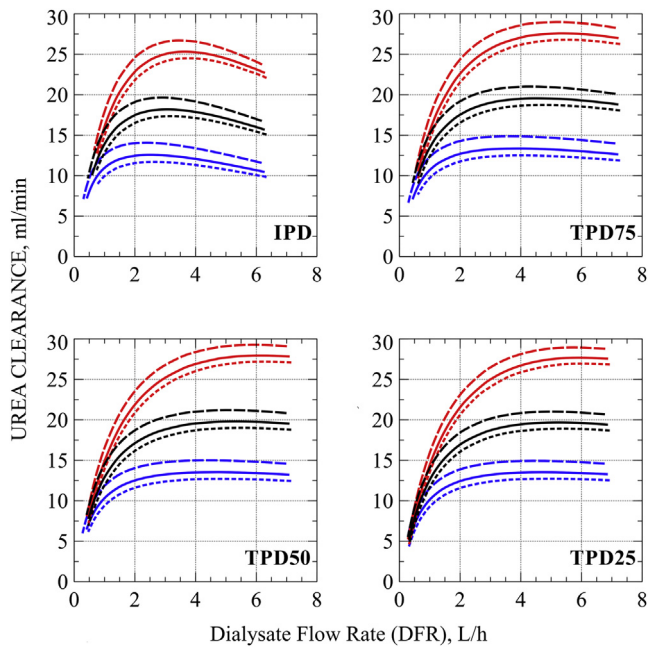


Figure 1. Simulated urea clearances as a function of dialysate flow rate (DFR) for the different techniques: intermittent peritoneal dialysis (IPD) and tidal peritoneal dialysis 75%, 50%, and 25% (TPD75/50/25); different transport types: fast (red line), average (black line), and slow (blue line); and 3 different glucose concentrations: 1.36% (dotted line), 2.27% (solid line), and 3.86% (dashed line).

line), average (black line), and slow (blue line) for 3 different glucose concentrations: 1.36% (dotted line), 2.27% (solid line), and 3.86% (dashed line). At low to moderate dialysate flow rates (< 2–3 L/h) the intermittent technique provides slightly higher clearances than the tidal technique. For slow transporters, higher-volume flows become ineffective (i.e., reach a plateau) at lower DFRs compared to average and fast transporter types. Thus, for small-solute transport, there is little benefit in exceeding 2 L/h for a slow transporter. For the lower tidal volumes (TPD50 and TPD25), the urea clearance is lower in the leftmost part of the curve compared to that of the other modalities, demonstrating a relative inefficiency of low tidal volumes at lower DFRs. The rightmost value for each curve represents the maximal flow rate possible at the chosen fill and drain flow rates (i.e., all time is spent either filling or draining the peritoneal cavity) and is, expectedly, higher for the tidal technique. The results for the other small solutes, creatinine, sodium, and phosphate are very similar to the urea results (data not shown), although the transport of sodium more closely follow the UF curve (reflecting the fact that ~ 80% of sodium is transported via convection).

Osmotic Water Transport

In Figure 2, the osmotic water transport, or “UF”, per session hour is shown as a function of DFR.

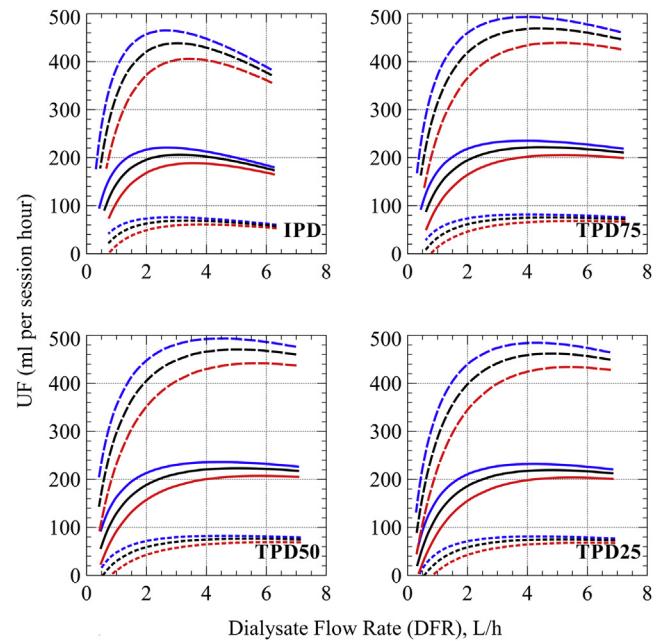


Figure 2. Osmotic water transport (ultrafiltration [UF]) per session hour as a function of dialysate flow rate (DFR) for the different techniques: intermittent peritoneal dialysis (IPD) and tidal peritoneal dialysis 75%, 50%, and 25% (TPD75/50/25); different transport types: fast (red line), average (black line), and slow (blue line); and 3 different glucose concentrations: 1.36% (dotted line), 2.27% (solid line), and 3.86% (dashed line).

Expectedly, in absolute terms, the UF is higher for the slow transporters due to the slower dissipation of glucose, improving the average osmotic pressure gradient. The peak values occur at similar DFRs compared to the urea clearance versus DFR curves in Figure 1. At first glance, this might seem a bit surprising, because it is at these DFRs that the glucose absorption is at its greatest. However, the increased glucose dissipation at these high DFRs will be more than well compensated by the influx of fresh dialysis fluid. Therefore the glucose gradient will be maintained despite increasing absorption. Thus it is the addition of fresh dialysis fluid that will increase both UF and clearance of small solutes at higher DFRs. The inefficiency at higher flows is due to the fact that, in relative terms, more time is spent filling and draining the peritoneal cavity, leading to a decrease in both UF and small-solute clearance. Again, fast transporters will benefit from slightly higher DFRs, whereas there is no benefit for slow transporters using DFRs > 2 L/h.

Osmotic Water Transport Efficiency

The osmotic transport of water (“UF”) during PD occurs at a “metabolic cost” in terms of glucose absorption. In Figure 3, the UF in milliliters per gram of glucose absorbed (or “UF efficiency”¹⁹) is plotted as a

function of DFR. The UF efficiency is markedly improved by increasing the DFR up to about 2 L/h, after which a plateau is reached and small or no further improvements are observed. For DFRs lower than 1 L/h, the UF efficiency drops rapidly. The higher glucose concentrations are far more efficient in achieving UF. Thus, at a DFR of 2 L/h, the patient will absorb more than twice the amount of glucose for the same amount of UF using the 1.36% solution compared to the 3.86% solution.

Small-Solute Transport Efficiency

In Figure 4, the small-solute transport efficiency (in millimoles of urea removed per gram of glucose absorbed) as a function of DFR is plotted. Similar to the osmotic efficiency above, the removal reaches an early plateau at DFRs higher than 2 L/h. However, concerning the glucose strength, the situation here is the opposite compared to the UF efficiency curves. The higher glucose concentrations are much less efficient in achieving urea transport. Thus, the patient will absorb almost twice the amount of glucose per millimole of urea removed using a 3.86% solution instead of a 1.36% solution. Apparently, for both UF and transport efficiency, there seems to be little benefit in increasing the DFR over 2 L/h.

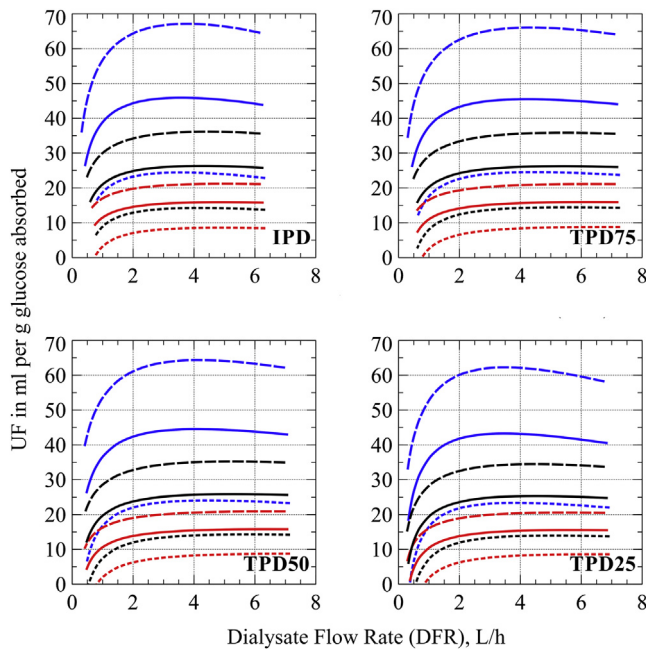


Figure 3. Osmotic water transport (ultrafiltration [UF]) in milliliters per gram of glucose absorbed (or “UF efficiency”) plotted as a function of dialysate flow rate (DFR) for the different techniques: intermittent peritoneal dialysis (IPD) and tidal peritoneal dialysis 75%, 50%, and 25% (TPD75/50/25); different transport types: fast (red line), average (black line), and slow (blue line); and 3 different glucose concentrations: 1.36% (dotted line), 2.27% (solid line), and 3.86% (dashed line).

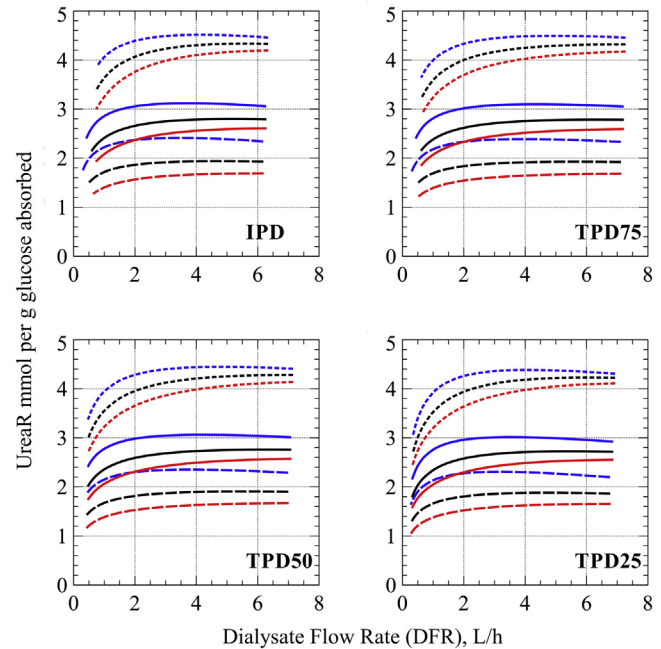


Figure 4. The small-solute transport efficiency (in millimoles [mmol] of urea removed per gram of glucose absorbed) as a function of dialysate flow rate (DFR) for the different techniques: intermittent peritoneal dialysis (IPD) and tidal peritoneal dialysis 75%, 50%, and 25% (TPD75/50/25); different transport types: fast (red line), average (black line), and slow (blue line); and 3 different glucose concentrations: 1.36% (dotted line), 2.27% (solid line), and 3.86% (dashed line).

Middle-Molecule Transport Versus DFR

In Figure 5, the clearance of β_2 -microglobulin as a function of DFR is shown. In comparison to the results for the small-solute transport, no peak or decrease in clearance was observed at higher DFRs for the tidal techniques. Furthermore, the smaller tidal volumes are clearly beneficial for middle-molecule transport.

Comparison With Clinical Studies

In Table 2, the extended TPM is compared with the study by Asarød *et al.*²⁰ There is good agreement between the model and the clinical measurements, although there appears to be a tendency for the model to underestimate the clearances at higher DFRs.

Osmotic Efficacy

The economic efficiency expressed in terms of UF per liter of dialysis fluid “consumed” as a function of DFR is shown in Figure 6 for the different techniques, transport types, and glucose concentrations. The maximum points to the left in the curves represent the lowest DFR at which the dialysis fluid will be efficient at removing water from the patient in terms of fluid consumption. In other words, Figure 6 reflects the simple fact that using a longer dwell time (a lower DFR) will increase the UF up to a certain point at which the amount of UF will start to decrease with dwell time. Similarly, increasing the DFR to very high values

Table 2. Comparison of clinical data for peritoneal dialysis (PD)

Dialysate flow rate	Intermittent PD Cl_{urea}	Tidal PD 50% Cl_{urea}
1.1 L/h	14.3 ^a ml/min (14.9)	13.3 ml/min (13.9)
1.6 L/h	16.9 ml/min (17.0)	15.9 ml/min (16.2)
2.7 L/h	20.9 ml/min (18.8)	19.9 ml/min (19.1)

Results from the clinical study by Asarød *et al.*, 1997²⁰ (average peritoneal equilibration test [PET] $D/P_{crea} = 0.77$) for intermittent PD and tidal PD 50% (TPD50) compared with the values predicted by the extended 3-pore model (in parentheses).
^a Cl_{urea} was significantly higher for intermittent PD in the clinical study. There were no significant differences in the 2 higher dialysate flow rates.

means that a lot of dialysis fluid is spent for very little UF. Thus, from an economical point of view, the highest osmotically efficacious DFR should be the maximum points in Figure 2. The intervals between the maximum points in Figure 2 and Figure 6 are thus osmotically efficacious and have been compiled in Table 3. It should be noted, however, that a DFR lower than ~ 1 L/h will lead to markedly increased glucose absorption (Figure 2).

Optimization Examples

The simulation results for UF efficiency and transport efficiency suggest that the overall glucose absorption can be decreased by alternating between short “UF dwells” and longer “solute removal dwells.” In Figure 7, a standard prescription of 6×2 L 1.36% glucose with a duration of 9 hours is compared with

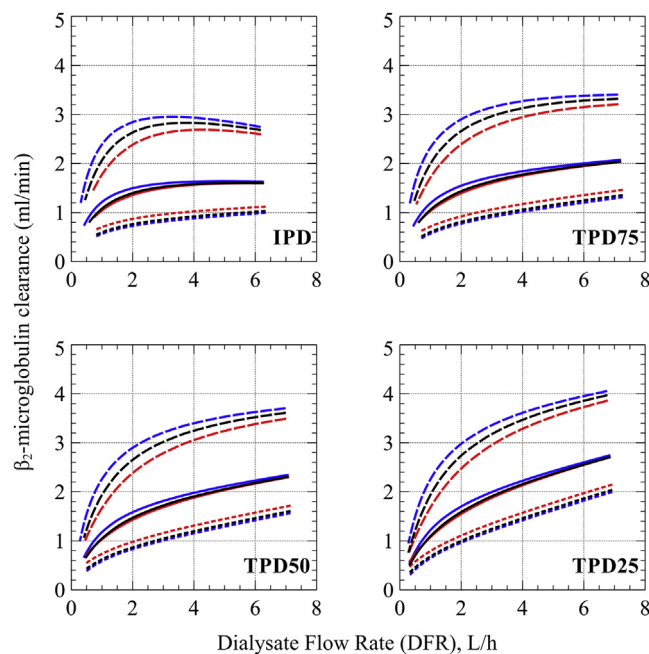


Figure 5. Clearance of β_2 -microglobulin as a function of dialysate flow rate (DFR) for the different techniques: intermittent peritoneal dialysis (IPD) and tidal peritoneal dialysis 75%, 50%, and 25% (TPD75/50/25); different transport types: fast (red line), average (black line), and slow (blue line); and 3 different glucose concentrations: 1.36% (dotted line), 2.27% (solid line), and 3.86% (dashed line).

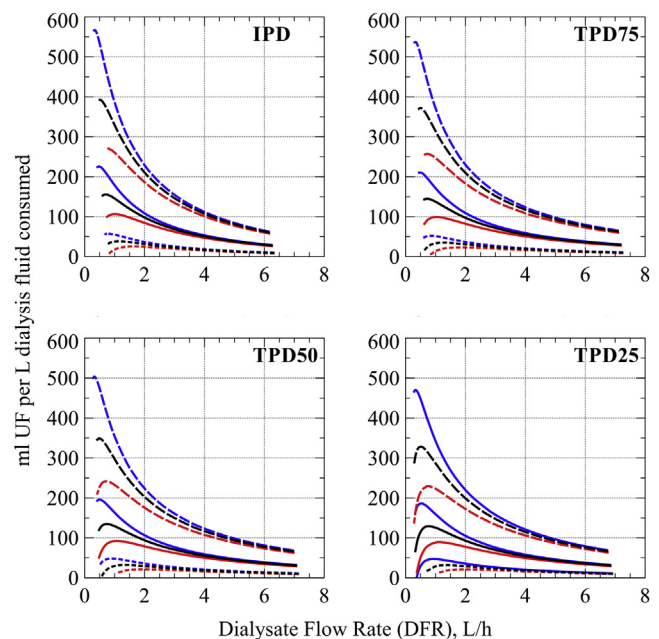


Figure 6. Osmotic water transport (ultrafiltration [UF]) in milliliters per liter of dialysis fluid “consumed” as a function of dialysate flow rate (DFR) for the different techniques, transport types, and glucose concentrations.

Table 3. Effective dialysate flow rate (DFR) intervals

Intermittent PD	Slow	Average	Fast
1.36%	0.8 L/h–2.8 L/h	1.1 L/h–3.3 L/h	1.6 L/h–3.9 L/h
2.27%	0.5 L/h–2.7 L/h	0.7 L/h–3.1 L/h	1.0 L/h–3.6 L/h
3.86%	0.3 L/h–2.7 L/h	0.5 L/h–3.1 L/h	0.7 L/h–3.5 L/h
75% Tidal PD	Slow	Average	Fast
1.36%	0.9 L/h–4.1 L/h	1.2 L/h–4.7 L/h	1.8 L/h–5.6 L/h
2.27%	0.5 L/h–4.1 L/h	0.7 L/h–4.5 L/h	1.0 L/h–5.2 L/h
3.86%	0.3 L/h–4.0 L/h	0.5 L/h–4.4 L/h	0.7 L/h–5.1 L/h
50% Tidal PD	Slow	Average	Fast
1.36%	0.9 L/h–4.6 L/h	1.3 L/h–5.4 L/h	1.8 L/h–6.3 L/h
2.27%	0.5 L/h–4.5 L/h	0.8 L/h–5.0 L/h	1.0 L/h–5.8 L/h
3.86%	0.3 L/h–4.7 L/h	0.5 L/h–5.0 L/h	0.8 L/h–5.8 L/h
25% Tidal PD	Slow	Average	Fast
1.36%	0.9 L/h–4.3 L/h	1.1 L/h–5.0 L/h	1.8 L/h–5.9 L/h
2.27%	0.5 L/h–4.2 L/h	0.7 L/h–4.8 L/h	1.0 L/h–5.6 L/h
3.86%	0.3 L/h–4.3 L/h	0.5 L/h–4.9 L/h	0.7 L/h–5.5 L/h

The lower limit represents the DFR at which a maximum ultrafiltration (UF) per liter of dialysis fluid used is attained (Figure 6). Using a lower DFR than this value will lead to less UF per liter of dialysis fluid spent. Also, DFRs lower than 1 L/h will markedly increase the glucose absorption in relation to the achieved UF (Figure 3). The upper limit of the interval is the DFR at which a maximum UF as a function of DFR is reached. Using a higher DFR will give less UF while spending more dialysis fluid. Note also that the peak values of the urea versus DFR curves (Figure 1) are very similar to the maximas of the UF versus DFR curves (Figure 2). PD, peritoneal dialysis.

scenarios in which each dwell is optimized for either UF (using 3.86% glucose) or small-solute transport (using 0% glucose), keeping the glucose absorption low. The treatment time for the 2 latter scenarios was chosen to fit the UF and urea transport of the “standard prescription.” The corresponding transport parameters

are shown in Table 4. Additional examples can be found in Supplementary Figures S1 and S2.

DISCUSSION

We have presented herein an extended TPM and applied it to a clinical problem: how to optimize APD with regard to maximizing UF and small-solute transport, and, at the same time, minimizing the metabolic cost in terms of glucose absorption. The computer simulations were performed for different techniques (IPD, TPD25/50/75), different transport types (slow, average, and fast), and 3 different glucose concentrations (1.36%, 2.27%, and 3.86%). To the best of our knowledge, these are the first simulations of this kind. We have demonstrated that the “metabolic cost” in terms of both urea removal and UF per gram of glucose absorbed is improved at somewhat higher DFRs (>2 L/h) than is usually prescribed. The relative inefficiency of increasing DFR above 3 L/h is demonstrated in these simulations, with the only exception being middle-molecular transport, which, according to the current results, is actually improved at higher DFRs and lower tidal volumes. It is also clear, from these simulations, that the metabolic efficiency, in terms of removal of small solutes per gram of glucose absorbed, is higher for lower glucose concentrations. The opposite holds true for UF in milliliters per gram of glucose absorbed, which is higher for higher glucose concentrations. These properties can be expected *a priori* simply on the basis of the difference in the clearance of glucose from the peritoneal cavity and the osmotic flux of water to the peritoneal cavity, and are not consequences of the TPM *per se*. Thus, relatively short “fluid removal dwells” containing a high glucose concentration take advantage of the fact that ultrafiltration is much larger in the initial part of the dwell, whereas longer “diffusion dwells” containing no glucose can be used to obtain sufficient small-solute removal using the fact that the reabsorption rate is far lower than the initial flow rates in a glucose-containing dwell.

In light of the increasing number of type 2 diabetic patients on PD treatment, the systemic glucose absorption associated with PD has become a growing

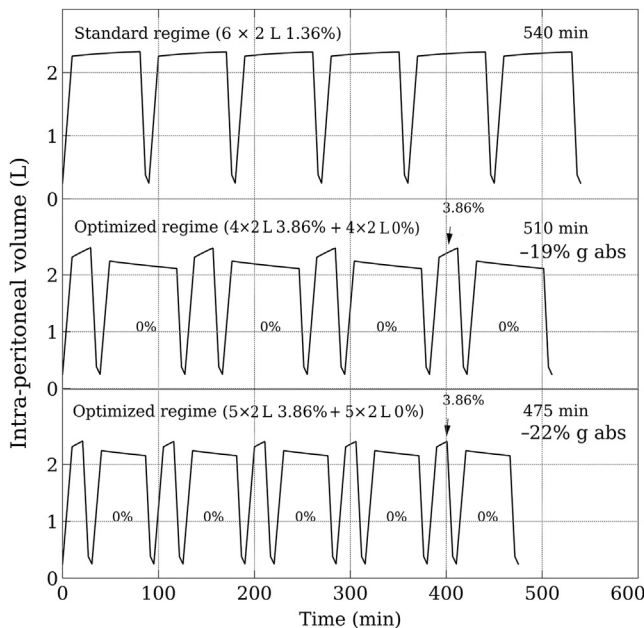


Figure 7. Simulated scenarios in which each dwell is optimized for either ultrafiltration (UF) (short dwells using 3.86% glucose) or small-solute transport (long dwells using 0% glucose) keeping the glucose absorption (abs) low. Corresponding transport parameters are shown in Table 4. Additional examples can be found in Supplementary Figures S1 and S2.

Table 4. Bimodal regimens compared with a standard 6 × 2 L regimen

Regimen	Urea removal	UF	Glucose absorption	Glucose Decrease	Total time
6 × 2 L 1.36%	158 mmol	458 ml	41.5 g	0%	540 min
4 × 2 L 3.86% + 4 × 2 L 0.0%	158 mmol	456 ml	33.8 g	-19%	510 min
5 × 2 L 3.86% + 5 × 2 L 0.0%	157 mmol	457 ml	32.3 g	-22%	475 min

Simulated “bimodal” regimens in which each dwell is optimized for either osmosis (using 3.86% glucose) or small-solute transport (using 0% glucose) keeping the overall glucose absorption low. The intraperitoneal volume versus time curves for the different scenarios are shown in Figure 7. Additional examples can be found in Supplementary Figures S1 and S2. UF, ultrafiltration.

concern. However, although glucose-sparing techniques improve the metabolic control in diabetic patients, low-glucose regimens may apparently lead to an increased risk of extracellular fluid volume expansion,²¹ presumably due to the lower amount of UF associated with these regimens. Optimizing a single PD dwell will typically mean finding a balance between UF and small-solute removal. However, because APD is based on several subsequent dwells, this allows for optimizing single dwells for either solute transport (low or, preferably, no glucose) or UF (high glucose), keeping the glucose absorption as low as possible during each dwell. Thus, the fact that weak glucose solutions provide more solute removal per gram of glucose absorbed and strong glucose solutions provide more UF per gram of glucose absorbed¹⁹ can be used to optimize APD with regard to minimizing glucose absorption. Indeed, such a strategy will lead to higher glucose concentrations for the “UF-dwells” than would be used in a “balanced” approach, and exposing the peritoneal tissues to higher glucose concentrations may have undesired effects. On the other hand, the systemic glucose exposure is lower (Table 4), and the contact time with the stronger glucose solution can be kept relatively short (Figure 7).

In summary, the current simulations using an extended TPM indicate that the glucose absorption of APD prescriptions can be greatly reduced by using moderately higher dialysate flows and using a bimodal treatment regimen. The side effects of such a treatment regimen compared to standard regimens with higher glucose absorption are, however, not known. Further research should assess whether such optimized bimodal regimens are feasible and safe, inasmuch as the possible reduction in glucose absorption appears to be significant. By using DFRs higher than standard prescriptions (~ 1.5–2 L/h), improvements in small-solute clearance and UF are also possible, although the relative benefits in UF and Kt/V seem to be relatively small compared to the increased cost of the treatment. It would, however, appear that the current model slightly underestimates the urea clearance at higher DFRs. Of course, higher DFRs will achieve the same UF and urea removal in a shorter period of time compared to standard treatments, although at a higher consumption of dialysis fluid. By contrast, using DFRs lower than 1 L/h would appear to increase the glucose absorption in relation to the achieved UF and small-solute removal. Thus, according to the current results, considering both the metabolic cost in terms of glucose absorption per milliliter of UF and the efficiency of the treatment in terms of small-solute transport and UF, a “UF-efficient” and economical DFR for most patients should lie between 1 and 3 L/h.

DISCLOSURE

CMÖ is the inventor of a pending patent filed by Gambro Lundia AB (Baxter) based on the content in the current article and has also worked as a consultant for Baxter Healthcare. BR participated in a clinical trial with Fresenius Medical Care, and received speaker’s honoraria from Fresenius Medical Care and Baxter Gambro Healthcare at Lund.

ACKNOWLEDGMENTS

This study was supported by the Swedish Research Council (Grant 08285), the Swedish Heart and Lung Foundation, the Medical Faculty at Lund University, and a grant from Baxter Healthcare Corporation. The study was presented in part at EuroPD in Krakow, Poland, 2–5 October 2015.

SUPPLEMENTARY MATERIAL

Detailed Methods. A description of the numerical methods used, details on the regulation of fill and drain cycles, and simulation of intraperitoneal pressure.

Table S1. Glossary of symbols and abbreviations.

Figure S1. Optimized “bimodal” regimens using 5% glucose concentration. Simulated scenarios where each dwell is optimized for either UF (short dwells using 5% glucose) or small-solute transport (long dwells using 0% glucose) keeping the glucose absorption low. A reduction of up to 27% of the glucose absorption was obtained compared to the “standard prescription” (see Table 4).

Figure S2. Optimized “bimodal regimens using 6% glucose concentration. Simulated scenarios where each dwell is optimized for either UF (short dwells using 6% glucose) or small-solute transport (long dwells using 0% glucose) keeping the glucose absorption low. A reduction of up to 33% was attained.

Supplementary material is linked to the online version of the paper at <http://www.kireports.org>.

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