Development of a computer-aided diagnosis system for a new modality of renal replacement therapy: an integrated approach combining both peritoneal dialysis and hemodialysis

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Abstract

The authors developed a computer-aided diagnosis system that includes a simple clinical test for the chronic renal disease patient who needs an integrated approach that combines both peritoneal dialysis and hemodialysis (PD–HD therapy). In this case study, the system simulated and estimated the dialysis outcome, the ultrafiltration volume and nutritional analysis by employing a pharmacokinetic model, and assessed the peritoneal permeable enhancement that can be a grave complication with peritoneal dialysis. This system requires only a minimum amount of nursing time and may be able to predict the optimal treatment schedule for PD–HD therapy and provide therapeutic monitoring in long-term peritoneal dialysis.
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1. Introduction

The peritoneal dialysis (PD) and the hemodialysis (HD) are well-known as a renal replacement therapy (RRT) and have been widely used in the world since their clinical implementation for the support of many end stage renal disease (ESRD) patients [1–3]. These RRTs, remove metabolites and excess fluid from total body fluid to a dialysate, which is referred to as dialysis and ultrafiltration. The process of removal occurs via a membrane of the dialyzer or the peritoneum. When selecting one of these therapies for ESRD patients, one needs to consider the quality of life (QOL), clinical compliance and so on [4]. The RRT can provide a sufficient QOL to ESRD patients through the maintenance of a high residual renal function (RRF), since such patients easily achieve the therapeutic criteria that are recommended by the statistical analysis. In advanced countries, there is a tendency that most of the ESRD patients select HD as primary care of the RRT. Although the efficiency of dialysis and ultrafiltration on HD is higher than those on PD, the RRF is better preserved in patients on PD than patients on HD [5–15]. With PD, most of the patients that have preservation of RRF achieve a dialysis outcome and ultrafiltration volume that is necessary to maintain their homeostasis [12,13]. However, it decreases gradually over the duration of PD treatment since the tissue of the peritoneum degenerates due to the long-term exposure to the dialysate which includes a high glucose concentration [16,17]. Recently, Keshaviah et al. and Van Biesen et al. reported that in early stage renal failure, PD should be chosen as the best method for achieving RRT because of the better preservation of RRF and improvement of QOL [18–20]. Therefore in the future, the mainstream regimen for RRT may be an integrated approach that combines both PD and HD as a novel modality (PD–HD therapy). With this therapy, one chooses PD initially for RRT in the early stages of renal failure and this is followed by intermittent HD use due to the RRF decline, decreases of dialysis outcome and ultrafiltration volume over the duration of PD treatment. The ESRD patients need to maintain their homeostasis by depending on HD as a final primary care. Thus the therapeutic efficiency of HD compensates for the loss seen with PD. Moreover, PD–HD therapy can supply the opportunity of the long-term PD for patients who may have a negative HD response. Patients undergoing HD who are looking to increase their social activities desire a long-term PD–HD therapy. ESRD patients with circulatory diseases need to be prescribed a continuous PD–HD therapy that includes high dose PD therapy, because intermittent therapies enhance excess of body fluid volume. Thus ESRD patients have various background factors with regard to their therapeutic conditions, and medical staff must explore the possibility of better prescriptions for PD–HD therapy of each patient. In addition, it is indispensable and very important to accumulate clinical data for further analysis and diagnosis. In this paper, by employing numerical simulation techniques and pharmacokinetic models for RRT, computer software (PHD NAVI) specifically designed for the PD–HD therapeutic regimen was developed. A clinical test (PHD NAVI test) was undertaken, which collected the input data of the PHD NAVI. The authors have also assessed the validation of the PHD NAVI test and the PHD NAVI with regard to its clinical application. PHD NAVI is capable of accumulating clinical data, assessing peritoneal permeability, estimating time courses of uremic toxin concentrations in the plasma and so on. With PHD NAVI, we can suggest better prescriptions for PD–HD therapy based on these factors by employing computer simulation techniques. When homeostasis is not stable, patients have to bear psychic stress and physical pain during the transient states, and be given immediately an optimal prescription. It is very important in terms of therapeutic strategies that an automatic procedure for suggesting better prescriptions by employing PHD NAVI shortens the mental and physical unstable states than manual procedures that use the trial and error method. PD–HD therapy is a novel renal replacement therapy that has just been recommended by the 2003 Annual Dialysis conference

in Seattle, so that there are few clinical cases. Although case studies that measure the QOL of ESRD patients prescribed by PHD NAVI are required in the future, current data for PHD NAVI suggests that it is more useful with regard to increasing QOL of the ESRD patients undergoing the PD–HD therapy than that seen with manual procedures.

2. Materials and methods

The dialysis outcome and ultrafiltration volume for the PD–HD therapy were estimated by applying a pharmacokinetic model for RRT. The PHD NAVI test is designed to collect the essential input data that can be used to determine a set of unknown parameters in a kinetic model for RRT. Additionally it also consists of multiple dialysate samples, including two kinds of dialysate for which the osmotic pressure is different, i.e. a 360 mOsm/kg-solvent (Low PDSol'n) and a 400 mOsm/kg-solvent (Mid PDSol'n). The PHD NAVI software was developed with Delphi 7.0J® that implements a graphical user interface (GUI) in order to design the event driven software [21].

2.1. Kinetic models

Assuming the peritoneum is homogeneous, Popovich et al. showed that solute transport in PD can be explained by diffusion and convection between plasma and dialysate, and derived a set of mathematical models (Pyle–Popovich model) that simulate peritoneal transport quantitatively [22]. Once a set of unknown parameters in this model optimized using clinical data, one can mathematically design a treatment schedule. The model equations are as follows:

$$G - \frac{dV_B C_B}{dt} - C_{LR}C_B = \frac{dV_D C_D}{dt} = \dot{m}, \tag{1}$$

$$\dot{m} = KA(C_B - C_D) + Q_U(1 - \sigma)\bar{C}, \tag{2}$$

$$\bar{C} = C_B - f(C_B - C_D), \tag{3}$$

$$f = \frac{1}{\beta} - \frac{1}{\exp(\beta) - 1}, \tag{4}$$

$$\beta = \frac{Q_U(1 - \sigma)}{KA}, \tag{5}$$

$$Q_U = a_1 \exp(a_2 t) + a_3, \tag{6}$$

$$V_D = V_D(0) + \frac{a_1}{a_2}[\exp(a_2 t) - 1] + a_3 t, \tag{7}$$

$$V_B + V_D = V_B(0) + V_D(0), \tag{8}$$

where C_B and C_D are the well-mixed plasma and dialysate concentration (mg/mL), V_B and V_D are the total body fluid volume (TBFV) and dialysate volume (mL), respectively. V_B is estimated by employing Hume and Weyers equation [23]. K is the overall mass transfer coefficient (cm/min), and A is the effective area of the peritoneal membrane (cm^2). The product of K and A (KA) is known as the overall mass transfer area-coefficient (MTAC) (mL/min), $\dot{m}$ is the mass transfer rate between the plasma and dialysate

(mg/min), G is the generation rate of the metabolite of interest (mg/min), σ is the Staverman reflection coefficient (-), C_{LR} is the residual renal clearance (mL/min), $\bar{C}$ is the mean solute concentration in the membrane (mg/mL), f is the weight coefficient for plasma and dialysate concentrations (-), β is the Peclet number (-), Q_U is the net osmotic flow rate (mL/min), and a_1 (mL/min), a_2 (1/min) and a_3 (mL/min) are the ultrafiltration volume profile equation coefficients (UF coefficients). Among these equations, Eq. (6) as well as Eq. (7) the integral form of Eq. (6), is an empirical equation that is known to fit well with clinical fluid transfer data. Parameters G, KA, σ, a_1, a_2 and a_3 are unknown and need to be determined from the clinical data for each patient. The metabolite concentrations in plasma and dialysate were calculated for an entire dwelling period by using the approximated analytical solutions derived from assuming that all the parameters were constant within each piecewise period of time [24]. The ultrafiltration volume was estimated by using Eq. (7). The unknown parameters were determined by employing the modified Powell method that applies the approximated analytical solutions [25].

Assuming the total body fluid is a 1-compartment model, Sargent et al. has shown that the following equations (urea kinetic model) can quantitatively demonstrate the solute transport in HD by using the clearance between the plasma and dialysate [26]:

$$\frac{dV_B C_B}{dt} = G - C_{LD} C_B - C_{LR} C_B, \tag{9}$$

$$C_{LD} = \frac{C_{Bi} - C_{B0}}{C_{Bi}} Q_{B0} + Q_F, \tag{10}$$

where C_{LD} is the clearance of the dialyzer that is dependent on the condition of the clinical operation in the clinical cases (mL/min). C_{Bi} and C_{B0} are the metabolite concentrations in the plasma at the start and end of HD, respectively (mg/mL). Q_F is the ultrafiltration rate (mL/min). Once C_{LD} is set by using clinical data or a reference value, one can mathematically estimate the time course of the metabolite concentration in plasma during HD. Moreover, Eq. (9) can also estimate the time course of the metabolite concentration in plasma when there is no RRT, by setting the C_{LD} equal to 0 mL/min.

In terms of the nutritional analysis, the body surface area (BSA) was estimated by employing Gehan's Equation (m^2) [27], the protein equivalent of the nitrogen appearance rate (PNA) was estimated by Kopple's Equation (g/day) [28], and the lean body mass (LBM) was estimated by Keshaviah's Equation (kg) [29]. Furthermore, the PNA and the LBM were revised according to body weight, which is the so-called nPNA (g/kg/day) and the LBM/BW(%).

2.2. PHD NAVI Test

The input data for the PHD NAVI were a set of clinical data, which could be used to optimize a set of unknown parameters in the kinetic models quantitatively and qualitatively. PHD NAVI test was the data acquisition part of the PHD NAVI. The essential requirements for the design of the PHD NAVI test were as follows: (1) maximize QOL for patients and medical staff, (2) minimize a set of the clinical data, (3) avoid unnecessary hospitalization, (4) measure the mass balance data for 24 h, (5) estimate the generation rate of metabolites by using the mass balance data, and (6) consist of multiple dialysate samples that include both Low PDSol'n and Mid PDSol'n, and a plasma sample.

2.3. Treatment schedule

The PHD NAVI estimated dialysis outcome and ultrafiltration volume for an arbitrary treatment schedule by employing the numerical simulation technique. The treatment schedule consisted of three major RRT modalities in a weekly regimen that integrated an approach that combined both PD and HD and dialysis holiday (DH). A PD regimen set the daily exchange schedule for dialysate, which consisted of the number of the dialysate exchanges, osmotic pressure of the dialysate, infused dialysate volume and dwelling time of each exchange. The HD regimen set treatment time, ultrafiltration volume and metabolite clearance of the dialyzer.

2.4. Kinetic analysis

The PHD NAVI evaluated the dialysis outcome and the ultrafiltration volume of the arbitrary treatment schedule by using both the Pyle–Popovich model and the urea kinetic model. The dialysis outcomes applied the weekly clear space, which divided quantity of solute removal by metabolite concentration in plasma [30].

$$\mathrm{CS} = \frac{\sum_1^n V_\mathrm{D} C_\mathrm{D}}{C_\mathrm{B}} m + \frac{V_\mathrm{B} C_\mathrm{B}(1 - (\frac{V_\mathrm{B} - Q_\mathrm{F}\mathrm{TT}}{V_\mathrm{B}})^{(C_\mathrm{LD}/Q_\mathrm{F})})}{C_\mathrm{B}} l + \frac{V_\mathrm{U} C_\mathrm{U}}{C_\mathrm{B}} 7, \tag{11}$$

where CS is the weekly clear space (L), TT is the treatment time for one session on HD (min), n, m and l are the number of dialysate exchanges during PD, the number of days for PD and the number of days for HD, respectively. The total amount of the fluid removal summed the weekly urine volume and the total ultrafiltration volume of RRT modalities in a weekly regimen, which was estimated by PHD NAVI. PHD NAVI then estimated the time course of the metabolite concentrations in plasma after having prescribed an arbitrary treatment schedule by employing kinetic models for the RRT.

3. Results and discussion

A computer-aided diagnosis system that combined both the PHD NAVI test and the PHD NAVI was developed by employing numerical simulation techniques and pharmacokinetic models, which can estimate the dialysis outcome and ultrafiltration volume of an arbitrary prescription for PD–HD therapy. Vonesh and Haraldsson et al. reported that diagnosis systems for the design of treatment schedules for PD were very useful [31–33]. However, there was little requirement for such systems for PD–HD therapy since PD–HD therapy has not really been implemented clinically. Thus this may be the first presentation in the world of a prototype of a computer-aided diagnosis system that uses the PHD NAVI and the PHD NAVI test for PD–HD therapeutic regimens.

3.1. PHD NAVI test

The clinical test protocol can have a great influence on the specification of computer-aided diagnosis since complicated schedules can decrease QOL and clinical compliance in patients. Fig. 1 illustrates the PHD NAVI test that can collect the input data of the PHD NAVI. As per Fig. 1, the clinical data were collected and are shown in Table 1. The PHD NAVI test measured the mass balance data over 24 h in
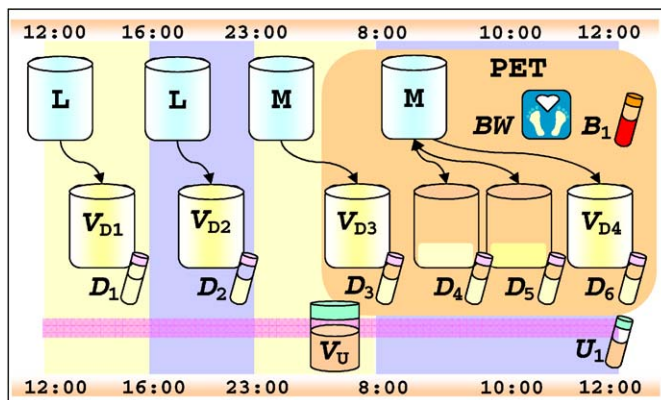
Fig. 1. Time table of the PHD NAVI test. L: Low PDSol'n, M: Mid PDSol'n, PET: Peritoneal Equilibration Test, BW: Body Weight, B_1: Blood Sample, $V_{D1}-V_{D4}$: Drainage volumes, D_1-D_6: Drainage samples, U_1: Urine sample, V_U: Urine volume.

Table 1
Input data on a female patient for the PHD NAVI

Blood sample			Urine sample			
# B	UN (mg/dL)	Creatinine (mg/dL)	# U	UN (mg/dL)	Creatinine (mg/dL)	Volume (mL)
1	74.0	14.0	1	41.0	12.0	170

Dialysate samples				
# D	UN (mg/dL)	Creatinine (mg/dL)	Drain volume (mL)	Dwell time (min)
1	55.0	8.5	2090	180
2	70.0	11.0	1940	360
3	73.0	13.4	2080	500
4	9.0	1.0	—	1
5	48.0	7.2	—	120
6	67.0	10.0	2250	240

She had a height of 159.5 cm and weight of 51.8 kg.
Infused dialysate volume of single exchange was 2.0 L.

consideration of the circadian rhythm of the patients. The appearance generation rate of metabolites was estimated by applying the mass balance data. The residual renal clearance was calculated by using the urine data.

The patient whose peritoneal permeability is enhanced, so called high-transporter shows a deficiency of the ultrafiltration volume in regimen with only Low PDSol'n. High-transporters should be given Mid PDSol'n, which increases the quantity of the solute and fluid removal via the peritoneum, in order to compensate a deficiency of the ultrafiltration volume. Therefore, the exchange schedule of dialysate
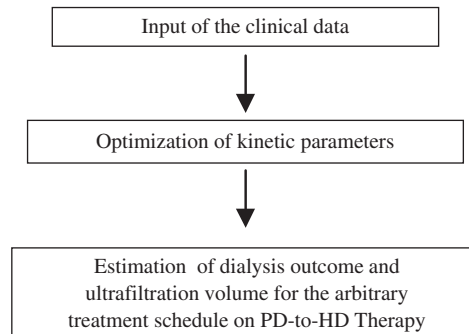
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┌─────────────────────────────────────┐
│      Input of the clinical data     │
└─────────────────────────────────────┘
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│    Optimization of kinetic parameters│
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│   Estimation  of dialysis outcome and│
│  ultrafiltration volume for the arbitrary│
│  treatment schedule on PD-to-HD Therapy│
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Fig. 2. Procedure for estimation of dialysis outcome and ultrafiltration volume.

in the PHD NAVI test consisted of multiple dialysate samples including both Low PDSol'n and Mid PDSol'n, for which the dwelling time of each exchange was optimized in order to execute a better kinetic analysis. High-transporter had also often been given the hyperosmolality dialysate (High PDSol'n) which is 460 mOsm/kg-solvent. Recently however, the use of the High PDSol'n has been avoided as much as possible, because of the bioincompatibility of High PDSol'n with regards to their hyperosmolality and high lactate and glucose concentration [34,35]. As a result, the PHD NAVI and the PHD NAVI test did not consider the evaluation of therapies designed for use with High PDSol'n.

In PD, metabolite concentration in the plasma exhibits an almost steady state during a 24 h time period because of the continuous blood purification. Blood samples were obtained after the final drain of the dialysate in the PHD NAVI test. In addition, the fourth dialysate exchange in the PHD NAVI test incorporated the Peritoneal Equilibration Test (PET), which assesses qualitative peritoneal permeability by applying the Mid PDSol'n and blood sample as shown in Fig. 1 [36]. Therefore, the PHD NAVI could estimate the residual intraperitoneal fluid volume and evaluate the mass transfer of the peritoneum qualitatively. If the patient is able to maintain clinical compliance, one can avoid unnecessary hospitalizations.

The metabolite clearances and ultrafiltration rate for HD depend on the individual clinical cases and are arbitrary compensational conditions with regard to the PD–HD therapy, so that these kinetic parameters do not need to be determined by using the PHD NAVI test.

Complicated clinical tests usually cause compliance problems, and thus make it harder to accurately examine the daily clinical outcome. The number of dialysate exchanges in the PHD NAVI test was four times during a 24 h period, which was nearly equal to ordinary prescriptions for PD. Therefore, the PHD NAVI test represents a good clinical path that can be skillfully used to obtain the essential clinical data for analysis of PD–HD therapy without any decline of QOL and clinical compliance by the patient and staff.

3.2. Kinetic models

The validations of the Pyle–Popovich and the urea kinetic models have been demonstrated through application to clinical cases [22,25]. Therefore,the PHD NAVI used to implement these models simulates the solute and fluid removal of PD–HD therapy qualitatively and quantitatively. Fig. 2 shows a series of procedures in which the PHD NAVI estimates the dialysis outcome and the ultrafiltration volume of an arbitrary treatment schedule. The estimation of the weekly dialysis outcome and ultrafiltration volume

Fig. 3. The analysis of the fluid removal. This illustrated a snapshot on the PHD NAVI, which was applied to the Table 1. BSA: Body surface area, TBFV: Total body fluid volume, InfV: Infused volume, RPV: Residual intraperitoneal fluid volume, a_1, a_2, a_3 are ultrafiltration profile equation coefficients.

continuously employed these kinetic models that used metabolite concentrations in the plasma to design the weekly treatment schedule.

These kinetic models that could apply the approximated analytical solution were also useful for the optimization method of a set of unknown kinetic parameters. The modified Powell method required no calculation of derivatives, so that the number of essential clinical data used by the method for the approximated analytical solution was smaller than that of the other conventional optimization methods. As a result, the PHD NAVI test can adopt a very simplified clinical path.

3.3. Kinetic analysis

An ideal solution for PD–HD therapy is where HD can be used as a supplement during the decline of dialysis outcome and ultrafiltration volume that occurs when PD is used alone. The PHD NAVI can analyze the peritoneal permeability of each patient by employing the kinetic models before considering what would be a better prescription for the PD–HD therapy. As can be seen in Table 1, PHD NAVI was used to execute a series of kinetic analyses for the patients.

Fig. 3 shows the analysis of the fluid removal, which was estimated by BSA, TBFV, residual intraperitoneal fluid volume (RPV), and UF coefficients for Low PDSol'n and Mid PDSol'n. Since the BSA is nearly equal to the area of the glomerulus filtration, it is one of the conditions which could be used to give the optimal hollow fibers surface area of dialyzer for HD to patients who select HD for the first time. The RPV can be used to diagnose intraperitoneal technical failure when there is trouble with the peritoneal catheter. The dialysis outcome and ultrafiltration volume during PD decreased with the increase of the RPV. There is a correlation for a_3 with the final reabsorption rate of the fluid from the intraperitoneal cavity to total body fluid, and thus it may be indicative of the lymphatic absorption rate quantitatively. The ultrafiltration volume decreased with increasing the lymphatic absorption. The intermittent oral administration of a low dose of tranexamic acid may suppress the lymphatic absorption, so that analysis of lymphatic reabsorption rate would be important [37]. Fig. 4 illustrates the time courses of the estimated intraperitoneal ultrafiltration volume (UF profile) for Low PDSol'n and Mid PDSol'n. The estimated profile of the determined parameters was in agreement with the clinical data. Thus the estimated UF profile
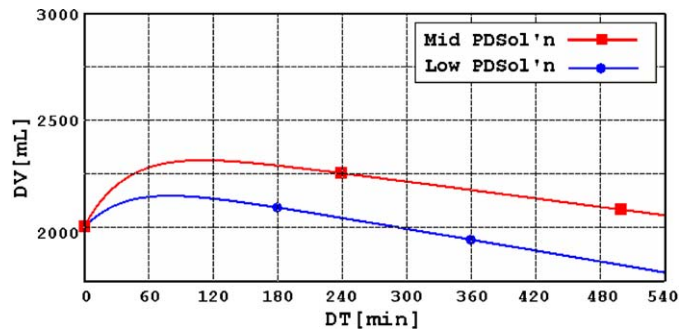
Fig. 4. The time courses of estimated intraperitoneal dialysate volume (UF profile). This illustrated a snapshot on the PHD NAVI. The time courses were the ultrafiltration volume with prescribing the Low PDSol'n and Mid PDSol'n in Table 1. DV: Drainage volume, DT: Dwell time.

Fig. 5. The analysis of the solute removal and nutritional adequacy. This illustrated a snapshot on the PHD NAVI, which was applied to the Table 1. GR: Generation rate, nPNA: normalized protein equivalent of the nitrogen appearance rate, LBM/BW: Lean body mass/body weight, UN: Urea nitrogen, Crea: Creatinine, MTAC: overall mass transfer area coefficient, RC: Staverman's reflection coefficient.

can be useful for the design of the schedule for dialysate exchange when considering the increase of the ultrafiltration volume.

Fig. 5 shows the analysis of the solute removal, which was estimated by the appearance generation rate, nPNA, LBM/BW, MTAC and the Staverman reflection coefficient. The nPNA is the index of the daily-required protein intake, and the LBM/BW is one of the daily activities with respect to the QOL. The recommendations for the nPNA and the LBM/BW with regard to RRT have been presented in the NKF-DOQI guidelines [13]. MTAC for small molecules such as urea and creatinine can quantitatively be used to evaluate the peritoneal permeability because the Peclet number for them is much lower than for other larger molecules. Fig. 6 illustrates the time course of the estimated peritoneal transport in which the metabolite concentration in the dialysate is divided by that in the plasma (D/P profile). The estimated
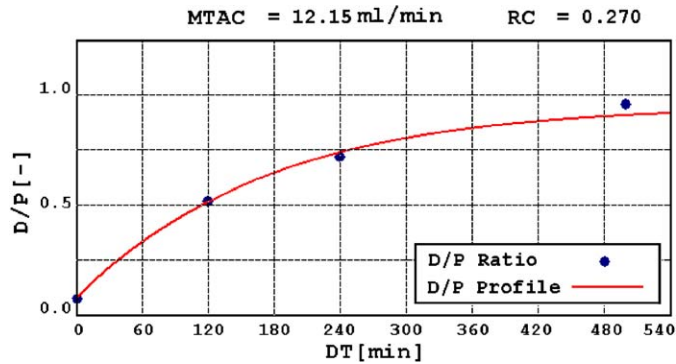
Fig. 6. The time course of estimated peritoneal transport which metabolite concentration in dialysate divided by that in plasma (*D/P* profile). This illustrated a snapshot on the PHD NAVI. The time course was the peritoneal transport of creatinine with prescribing the Mid PDSol'n in Table 1. D/P: metabolite concentration in dialysate / that in plasma, DT: Dwell time.

Fig. 7. The essential conditions for design of the treatment schedule. This illustrated a snapshot on the PHD NAVI. Treatment schedule adopted the condition of #P2 in Table 2. PD: Peritoneal dialysis, HD: Hemodialysis, Holiday: Dialysis holiday, InfV: Infused volume, DT: Dwell time, TT: Treatment Time, UFV: Ultrafiltration volume, UN_CL: Clearance for urea nitrogen, Cr_CL: Clearance for creatinine.

D/P profile found by using a set of determined parameters showed much a smaller discrepancy with the clinical data. Thus, the D/P profile can be useful for reconstruction of the schedule of dialysate exchange when considering the increase of the dialysis outcome.

Fig. 7 shows the essential conditions for the design of the treatment schedule. The Weekly Dialysis Schedule in Fig. 7 can be used to register a weekly regimen for the PD–HD therapy, by selecting one of the modalities that is, PD, HD or DH on a daily basis. The days that either HD or DH are scheduled
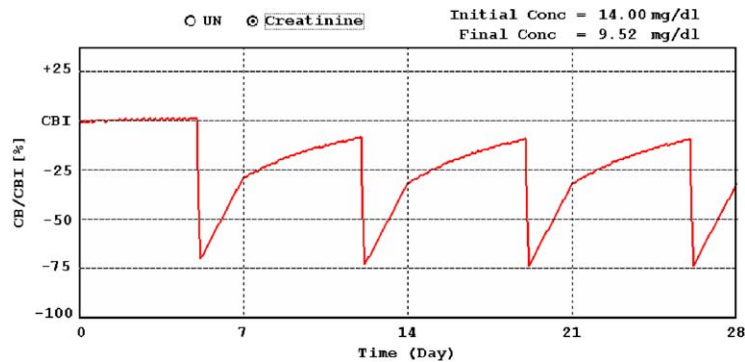
Fig. 8. The time course of the estimated creatinine concentration in plasma. This illustrated a snapshot on the PHD NAVI. Treatment schedule adopted the condition of #P2 in Table 2. CB: Metabolite concentration in plasma, CBI: Initial metabolite concentration in plasma.

are referred to as Peritoneal Rest. These days may help to suppress the decline of the dialysis outcome and ultrafiltration volume during PD, by preventing exposure of the peritoneum to the hyperosmolarity dialysate [38,39]. Fig. 7 shows a schedule that has one day for HD and DH after 5 consecutive days with PD.

The Daily PD Schedule seen in Fig. 7 consists of the number of the dialysate exchanges for each day, osmotic pressure of the dialysate, and the infused volume and dwelling time of each exchange. The ordinary treatment schedule for PD may differ from that in the PHD NAVI test, and moreover, the infused dialysate volume and osmotic pressure may be prescribed in an arbitrary combination in individual clinical cases. The solute removal that depends on the MTAC during PD increases with an increase of infused dialysate volume because of the expansion in the effective surface area of the peritoneum. Spencer and Farrell reported that the MTAC for humans increased 1.2-fold when infused dialysate volume was increased from 1000 to 2000 mL [40]. Considering the relation to the infused dialysate volume differs from that in the PHD NAVI test, we therefore calculated the solute removal by using the revised MTAC. On the other hand, the fluid removal volume during PD that depends on the osmotic pressure of the infused dialysate increases with an increase of the osmotic gradient between the intraperitoneal dialysate and plasma. The UF coefficients for the osmotic pressure that differ from those in the PHD NAVI test were determined by considering the proportional rate of Low PDSol'n and Mid PDSol'n with regard to the differences. Therefore, PHD NAVI can be used to estimate and assess the therapeutic efficiency of the arbitrary schedule for PD. In Fig. 7, the number of dialysate exchanges is 4, with 400 mOsm/kg-solvent dialysate (Mid PDSol'n), and each dwelling time for the series was 360 min. The infused dialysate volume for the series was 2000 mL.

The HD Operation in Fig. 7 consisted of the treatment time, the ultrafiltration volume and the metabolite clearance of the dialyzer for one session. The ultrafiltration rate in Eq. (10) was calculated by dividing the ultrafiltration volume by the treatment time. The clearance of the dialyzer was calculated by employing Eq. (10) or cited the reference value. The parameters for HD in Fig. 7 are typical of conditions in Japan.

The validation of the prescription for the PD–HD therapy was assessed by the estimated weekly quantity of the solute and fluid removal. Moreover, the time course of the metabolite concentration in the plasma was numerically simulated by employing kinetic models for RRT (Figs. 8 and 9). The time course of
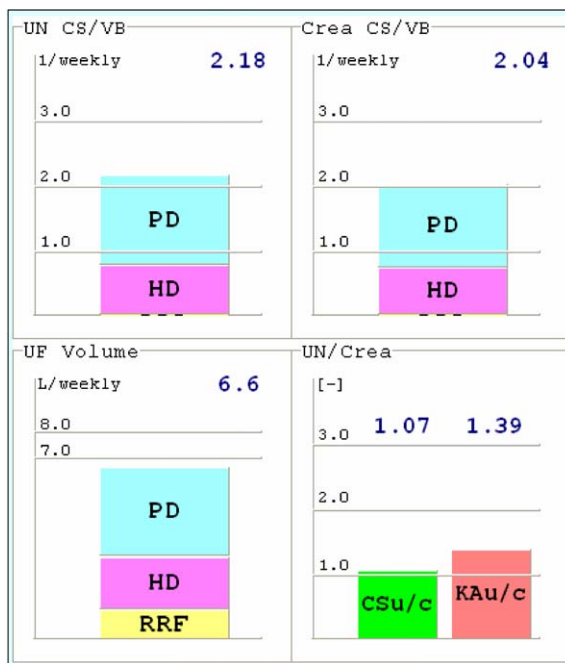
Fig. 9. The analysis for the Dialysis outcome, ultrafiltration volume and peritoneal permeability. This illustrated a snapshot on the PHD NAVI. Treatment schedule adopted the condition of #P2 in Table 2. CS/VB: Clear space / total body fluid volume, RRF: Residual renal function, CS$u/c$: CS/V_B for urea nitrogen/CS/V_B for creatinine, KAu/c: MTAC for urea nitrogen/MTAC for creatinine.

the metabolite concentration in plasma declined gradually with the increase in the quantity of solute and fluid removal. The quantity of solute removal during the PD–HD therapy was evaluated by using both the CS and the CS/V_B, which divides CS by total body fluid volume. The peritoneal permeability and the quantity of solute removal with PD were also assessed by using the KAu/c, which divides the MTAC for urea nitrogen by that for creatinine. The quantity of the fluid removal was estimated by adding both a weekly ultrafiltration volume of the RRT and urine volume.

The CS represented the purified body fluid volume on the PD–HD therapy, and was useful for the evaluation of the therapeutic efficiency. However, CS has not been normalized as a universal therapeutic index, so that we had to seek out an appropriate allowance for individual clinical cases. The PHD NAVI evaluated the solute removal by employing the CS/V_B, which may cancel out individual differences between patients. The CS/V_B was a dimensionless parameter, and may set the criterion that is common to all patients. The Kt/V_B implemented for PD was quantitatively similar to the CS/V_B, which also divides the purified body fluid volume by total body fluid volume [41]. In the NKF-DOQI guidelines, the criterion for weekly Kt/V_B for urea nitrogen was recommended to be more than 2.0 [13]. This indicates that the weekly purified fluid volume is more than 2.0-fold of the total body fluid volume. The weekly CS/V_B for urea nitrogen during HD with 3 sessions per week as determined by the urea kinetic model also might be more than 2.0 in many cases. Therefore, the recommendation for the CS/V_B for PD–HD therapy might be more than 2.0. Moreover, the CS$u/c$ was the ratio of the clear space for creatinine to that

Table 2
Numerical simulation on the PD–HD therapy

#	PD (day)	HD (day)	DH (day)	CS/V_{Bu}[a] (—)	CS/V_{Bc}[b] (—)	FRV[c] (L)
P1	7	0	0	1.97	1.83	6.0
P2	5	1	1	2.18	2.04	6.6
P3	6	1	0	2.46	2.30	7.3

[a]Weekly CS/V_B for urea nitrogen.
[b]Weekly CS/V_B for creatinine.
[c]Weekly fluid removal volume (Ultrafiltration + Urine).

for urea nitrogen, and represented the intensity of the PD–HD therapy. CSu/c was gradually decreased to 1.0 with increases in the purified body fluid volume.

The KAu/c was the ratio of the peritoneal permeability for creatinine to that for urea nitrogen, and was a dimensionless parameter similar to the CS/V_B. The KAu/c was gradually decreased to 1.0 with enhancement of the peritoneal permeability. The driving force of the ultrafiltration on PD depends on the osmotic gradient between intraperitoneal dialysate and plasma, so that the KAu/c may correlate with the ultrafiltration volume. The evaluation of MTAC for glucose, which is the osmotic agent in PD, has not been implemented in clinical use because the circadian rhythm for the metabolic rate for glucose is unstable and has a weak reproducibility. Molecular weight of the urea nitrogen, creatinine and glucose was 60, 113 and 180, respectively, which exhibited an approximate gradation relationship. Yamashita et al. reported that the MTAC for small molecules showed linearity to molecular weight [42]. Therefore, KAu/c should evaluate the ultrafiltration volume as well as the dialysis outcome. One can easily prescribe and assess the peritoneal permeability and the treatment schedule for the PD–HD therapy by using both the CS/V_B and the KAu/c, although the criteria for these need to be investigated in detail by a further clinical study.

3.4. Simulation

Table 2 shows the estimated dialysis outcome and ultrafiltration volume obtained by employing the PHD NAVI with the typical Japanese clinical data that was presented in Table 1. In PD, the number of dialysate exchanges was 4 with 400 mOsm/kg-solvent dialysate, and each dwelling time for the series was 360 min. The infused dialysate volume for the series was 2000 mL. The HD analysis used the typical conditions that were described in Fig. 7. As seen in Table 2, #P1 was scheduled for 7 days of PD. For #P2, there was one day of HD and DH after for 5 days of PD, (which is indicated in Fig. 7), and for #P3 there was one day of HD after 6 days of PD. The CS/V_B for creatinine and the ultrafiltration volume for #P2 increased 1.1-fold over that seen for #P1. Moreover of the values for #P3 increased at least 1.2-fold over those seen for #P1. The CS/V_B for small molecules such as urea and creatinine during PD are approximately proportional to the relation to drainage dialysate volume. Although one can prescribe a high dose treatment and/or the High PDSol'n, the QOL of the patient declined with the increase of the infused dialysate volume. Moreover, in ESRD patients having no RRF during PD, they were not able to achieve any better outcomes similar to the 1.2-fold increases of the dialysis outcome and ultrafiltration volume that are seen in current prescriptions. On the other hand, the dialysis outcome and ultrafiltration

volume with the use of HD for one session resulted in an increase of at least 2.0-fold of those with a current prescription for PD for one day. Therefore, the PD–HD therapy can increase the dialysis outcome and the ultrafiltration volume in ESRD patients, and supply the peritoneal rest and the dialysis holiday for patients. The PHD NAVI and the PHD NAVI test are designed to bring about an optimal therapeutic strategy for the PD–HD therapy, with migration from PD to HD occurring gradually by increasing the number of weekly sessions of HD.

In addition, the PHD NAVI and the PHD NAVI test may be able to assess the follow-up of encapsulating peritoneal sclerosis (EPS), which is a very grave complication of PD. Long-term PD had been one of major risk factors that contributes to EPS, thus follow-up for EPS is necessary during long-term PD. The symptom of EPS include peritoneal permeable enhancement such as that seen with high transporters [43,44]. The PHD NAVI can evaluate the peritoneal permeability with *KAu/c*, so one may be able to observe the peritoneal physiological degradation by using the time course of the *KAu/c* during long-term PD. The PHD NAVI can support high quality medical treatment, which leads to a better prescription for the PD–HD therapy during the observation of the symptom of EPS.

4. Summary

The RRT for ESRD patients has been reviewed with respect to the RRF by many researchers in the world. In the future, most of the ESRD patient prescribed peritoneal dialysis for primary care will be introduced to an integrated approach that combines peritoneal dialysis and hemodialysis, the so-called PD–HD therapy. And in the future PD–HD therapy may become one of the main regimens recommended for ESRD patients. However, it may be difficult for PD–HD therapy to stabilize the therapeutic efficiency and QOL for patients. Although medical staffs and patients need to observe and estimate the dialysis outcome and ultrafiltration volume during PD–HD therapy for the entire therapeutic duration, they currently have no useful tools for diagnoses. Therefore, a therapeutic monitoring system needs to be implemented in preparation for a proposal of using PD–HD therapy as a novel modality.

The authors have developed a computer-aided diagnosis system that can observe and assess dialysis outcome and ultrafiltration volume during PD–HD therapy by employing a pharmacokinetic model for RRT. This system consists of the PHD NAVI test that collects the essential clinical data and the PHD NAVI that evaluates the therapeutic efficiency, peritoneal permeability and homeostasis of patients on PD–HD therapy. Since the procedure for the PHD NAVI test is the same as that for ordinary therapeutic schedules of PD patients, the PHD NAVI test is a good clinical path that is able to obtain clinical data for kinetic analysis of the PD–HD therapy without causing declines in the QOL of patients and medical staffs. The PHD NAVI can easily estimate the dialysis outcome, ultrafiltration volume, nutritional analysis and peritoneal permeability for PD–HD therapy by employing both the computer graphical user interface and numerical simulation techniques. Moreover, the PHD NAVI can use the CS/V_B and the *KAu/c* in order to assess enhancement of the peritoneal permeability and dialysis outcome. These novel indexes that are derived from pharmacokinetics may be useful for the design of treatment schedules for PD–HD therapy and the assessment for the follow-up of encapsulating peritoneal sclerosis that is one of the grave complications of peritoneal dialysis. This system requires a minimum amount of nursing time and may be able to suggest an optimal treatment schedule for PD–HD therapy and provide therapeutic monitoring during long-term PD.

Acknowledgements

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