INTERMITTENT PERITONEAL DIALYSIS: UREA KINETIC MODELING AND IMPLICATIONS OF RESIDUAL KIDNEY FUNCTION

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♦ **Background:** Intermittent peritoneal dialysis (IPD) is an old strategy that has generally been eclipsed, in the home setting, by daily peritoneal therapies. However, for a select group of patients with exhausted vascular access or inability to receive PD at home, in-center IPD may remain an option or may serve as an incremental strategy before initiation of full-dose PD. We investigated the residual kidney clearance requirements necessary to allow thrice-weekly IPD regimens to meet current adequacy targets.

♦ **Methods:** The 3-pore model of peritoneal transport was used to examine 2 thrice-weekly IPD dialysis modalities: 5 – 6 dwells with 10 – 12 L total volume (low-dose IPD), and 50% tidal with 20 – 24 L total volume (high-dose IPD). We assumed an 8-hour dialysis duration and 1.5% dextrose solution, with a 2-L fill volume, except in tidal mode. The PD Adequest application (version 2.0: Baxter Healthcare Corporation, Deerfield, IL, USA) and typical patient kinetic parameters derived from a large dataset [data on file from Treatment Adequacy Review for Gaining Enhanced Therapy (Baxter Healthcare Corporation)] were used to model urea clearances. The minimum glomerular filtration rate (GFR) required to achieve a total weekly urea Kt/V of 1.7 was calculated.

♦ **Results:** In the absence of any dialysis, the minimum residual GFR necessary to achieve a weekly urea Kt/V of 1.7 was 9.7 mL/min/1.73 m². Depending on membrane transport type, the low-dose IPD modality met urea clearance targets for patients with a GFR between 6.0 mL/min/1.73 m² and 7.6 mL/min/1.73 m². Similarly, the high-dose IPD modality met the urea clearance target for patients with a GFR between 4.7 mL/min/1.73 m² and 6.5 mL/min/1.73 m².

♦ **Conclusions:** In patients with residual GFR of at least 7.6 mL/min/1.73 m², thrice-weekly low-dose IPD (10 L) achieved a Kt/V urea of 1.7 across all transport types. Increasing the IPD volume resulted in a decreased residual GFR requirement of 4.7 mL/min/1.73 m² (24 L,

50% tidal). In patients with residual kidney function and dietary compliance, IPD may be a viable strategy in certain clinical situations.

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Intermittent peritoneal dialysis (IPD) has occasionally been used to deliver long-term renal replacement therapy or as an in-center “bridge” therapy for the new patient not trained in self care (1,2). In-center IPD can be considered a type of “assisted” peritoneal dialysis (PD) that offers an additional treatment option in countries not having reimbursement mechanisms that allow for assisted PD in the home. Intermittent PD could also be considered an “incremental PD” strategy.

The total burden of end-stage renal disease continues to rise, including patients with many advanced comorbidities and patients who were previously on hemodialysis and who have exhausted available vascular access. Many of these patients are likely to be unable to perform PD, limiting their therapeutic options. Providing in-center assistance with a thrice-weekly PD regimen, similar to a traditional hemodialysis (HD) schedule, may be an attractive option for this needy population.

Many long-term patients and most new dialysis patients maintain significant residual kidney function (RKF) that contributes to total weekly solute and fluid removal. Patients with significant RKF can initiate dialysis using an incremental regimen based on the significant contribution of RKF to meeting adequacy targets (3,4). We sought to better understand the contribution of RKF in the application of thrice-weekly IPD therapy. Specifically, by using typical patient kinetic parameters derived from a large dataset [data on file from Treatment Adequacy Review for Gaining Enhanced Therapy (TARGET: Baxter Healthcare Corporation, Deerfield, IL, USA)],

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we investigated the RKF requirements that would allow thrice-weekly IPD to meet current weekly urea clearance targets for PD (5).

METHODS

Three clinical presentations were modeled (Figure 1). In patients not on dialysis, the minimum residual GFR necessary to achieve the recommended adequacy target—that is, a total weekly urea Kt/V of 1.7—was calculated (5). The 3-pore model of peritoneal transport was used to estimate peritoneal clearances for a range of conditions with an increasing dose of dialysis. Based on these weekly (that is, 7 days/week) values, values for thrice-weekly IPD were estimated.

CALCULATION OF PERITONEAL CLEARANCE AND GFR

The patient kinetic parameters were obtained from data submitted to Baxter Healthcare Corporation's Renal Division in 1999 by centers around the United States and Canada participating in the TARGET national adequacy initiative (data on file). The centers collected data from patients undergoing a 4-hour peritoneal equilibration test (PET) at the end of a long overnight exchange. These data were then voluntarily sent to the Renal Division for analysis. Data from approximately 1200 patients were collected. To obtain average kinetic parameters, the data

were first grouped into the four PET categories [high (H), high-average (HA), low-average (LA), low (L)] according to 4-hour measurements of dialysate-to-plasma (D/P) creatinine (6). Using the PD Adequest application (version 2.0: Baxter Healthcare Corporation), relevant kinetic transport parameters such as solute mass transfer area coefficient (MTAC, milliliters per minute), ultrafiltration (UF) coefficient (LPA, milliliters per minute per millimeter Hg), and transport surface area (A0/dX, centimeters) were first estimated for each patient. Four typical patients were then created to represent each PET category. This procedure was repeated for three levels of body surface area (BSA: <1.71 m², 1.71 – 2.0 m², and >2.0 m²). The parameters analyzed in the present study represent patients at the medium BSA level. The simulations were performed for each patient group individually. Weekly urea Kt/V was estimated for each therapy condition. Table 1 shows the relevant patient characteristics and kinetic parameters for urea, creatinine, and glucose.

The simulated therapy conditions were chosen such that the delivered dialysis dose was augmented incrementally to accommodate patients with a lower RKF. In addition to the reference condition of no dialysis, we investigated 2 thrice-weekly modalities:

- 5 – 6 automated PD dwells with 10 – 12 L fluid ("low-dose IPD"), and
- 50% tidal PD with 20 – 24 L fluid ("high-dose IPD").

We assumed an 8-hour dialysis duration, dialysate with a 1.5% dextrose concentration, and a 2-L fill volume

A) No dialysis

B) Three times per week IPD with 10 - 12L APD

C) Three times per week IPD with 20 - 24L, 50% Tidal PD

Figure 1 — Intermittent peritoneal dialysis (IPD) regimens modeled. APD = automated peritoneal dialysis.

TABLE 1

Kinetic Parameters for the Study Patients by Membrane Transport Category

Parameter	Transport category			
	H	HA	LA	L
Body surface area (m ²)	1.85	1.86	1.87	1.85
Total body water (L) ^a	40.6	41.3	42.3	40.6
4-h D/P creatinine	0.86	0.71	0.59	0.43
4-h D/D ₀ glucose	0.25	0.34	0.44	0.53
Urea MTAC (mL/min)	27.71	23.14	18.40	15.92
Creatinine MTAC (mL/min)	19.15	11.92	8.60	5.19
Glucose MTAC (mL/min)	16.34	11.71	8.35	5.96
LPA (mL min ⁻¹ mmHg ⁻¹)	0.0575	0.0560	0.0492	0.0554
A0/dX (cm)	40 398	29 362	21 942	16 402

H = high; HA = high-average; LA = low-average; L = low; D/P = dialysate-to-plasma ratio; D/D₀ = end-to-initial dialysate ratio; MTAC = mass transfer area coefficient; LPA = ultrafiltration coefficient; A0/dX = transport surface area.

^a By the Watson formula.

(except in tidal modeling). Tidal regimens were modeled to determine the clearances achievable with higher delivered total volumes and to provide data on an IPD regimen that could potentially reduce drain pain and prevent slow drain phases [which may reduce the efficiency of an IPD regimen (7)]. Figure 1 summarizes those conditions.

The values obtained from the PD Adequest 2.0 (8) calculation of weekly peritoneal urea Kt/V (Kt/V_p) were then adjusted using Equation 1 to determine the peritoneal urea Kt/V for thrice-weekly intermittent PD:

$$(Kt/V_p) \text{ of IPD} = (3 / 7) \times \text{Modeled weekly } (Kt/V_p) \quad [1]$$

This equation is most valid when serum urea concentrations do not vary substantially during the week—that is, when patients have significant RKF, and the dose of dialysis is low, as in the present study.

As previously suggested (9), the RKF weekly Kt/V (Kt/V_R) was determined by subtracting the Kt/V_p from the total Kt/V (Kt/V_T , where $Kt/V_T = 1.7$):

$$Kt/V_R = Kt/V_T - Kt/V_p \quad [2]$$

The RKF Kt/V values were then converted to residual urea clearances:

$$K_{R,UREA} \text{ (mL/min)} = Kt/V_R \times [TBW \times 1000 \text{ (mL)}] / [7 \times 24 \times 60 \text{ (min)}] \quad [3]$$

where TBW is total body water in liters calculated using the Watson formula.

Finally, residual GFR values were calculated according to the formula in the Dialysis Outcomes Quality Initiative (DOQI) guidelines:

$$\text{GFR (mL/min)} = (K_{R,CREATININE} + K_{R,UREA}) / 2 \quad [4]$$

where $K_{R,CREATININE} = 2 \times K_{R,UREA}$, which is an estimate derived from DOQI discussions and recommendations between 1995 and 1997 (10).

RESULTS

Table 2 summarizes the calculated per-week Kt/V_p for the thrice-weekly low- and high-dose IPD regimens. In simulated patients, the Kt/V_p was higher in patients with faster solute transport (H, HA) than in those with slower solute transport (L, LA). For instance, in the case of 24-L 50% tidal therapy, the weekly Kt/V_p varied between 0.84 – 0.87 (H, HA) and 0.60 – 0.64 (L, LA). Compared with the low-dose dialysis regimens, the high-dose regimens resulted in higher Kt/V_p values. For example, in patients with fast solute transport (H), the 24-L 50% tidal weekly Kt/V_p was 0.84 compared with 0.50 for 10-L automated PD. A similar trend was observed in patients with slow (L) solute transport: the Kt/V_p was 0.60 compared with 0.39. In the absence of any dialysis, the mean minimum residual GFR necessary to achieve a weekly urea Kt/V of 1.7 was 9.7 mL/min/1.73 m² (range: 9.6 – 9.9 mL/min/1.73 m²), as shown in Table 3. That value is within guidelines published by national and international expert nephrology groups

TABLE 2
Weekly^a Peritoneal Kt/V Calculated for Intermittent Peritoneal Dialysis (IPD) Therapies

Solution volume	IPD mode	Kt/V by transport category			
		H	HA	LA	L
10–12 L	APD	0.50–0.56	0.60–0.65	0.40–0.43	0.39–0.41
20–24 L	50% Tidal	0.76–0.84	0.81–0.87	0.59–0.64	0.56–0.60

H = high; HA = high-average; LA = low-average; L = low; APD = automated peritoneal dialysis.

^a For treatment delivered thrice-weekly.

TABLE 3
Calculated Residual Glomerular Filtration Rate (GFR) Necessary to Achieve a Total Weekly Kt/V Urea of 1.7

Solution volume	IPD mode	GFR (mL min ⁻¹ mmHg ⁻¹) by transport category			
		H	HA	LA	L
—	No dialysis	9.7	9.7	9.9	9.6
10 L–12 L	APD	6.8–6.5	6.3–6.0	7.6–7.4	7.4–7.3
20 L–24 L	50% Tidal	5.3–4.9	5.1–4.7	6.5–6.2	6.4–6.2

IPD = intermittent peritoneal dialysis; H = high; HA = high-average; LA = low-average; L = low; APD = automated peritoneal dialysis.

(6–10.5 mL/min/1.73 m²) to initiate dialysis (4). Intuitively, the minimum residual GFR might be thought to be independent of peritoneal membrane characteristics—that is, fast (H) or slow (L) transport. Although that understanding is fundamentally true, the Watson TBW depends on height, weight, and sex, and thus can be different for different patients, thereby affecting calculation of the RKF urea clearance ($K_{R,UREA}$)—and consequently the GFR. In the present study, the Watson TBW range among the simulated patients was 40.6–42.3 L.

The calculated minimum residual GFR also varied with patient type and dose of dialysis. As shown in Table 3, patients with slower solute transport required higher levels of GFR to achieve a weekly Kt/V of 1.7, regardless of dialysis regimen. As the dialysis dose increased, the required GFR decreased for all patients (Table 3).

DISCUSSION

The results of the present study demonstrate that, in patients with significant remaining RKF, adequate urea removal can be achieved during thrice-weekly IPD. Modeled Kt/V targets of 1.7 could be achieved with IPD volumes of 10–12 L administered to patients with a GFR of 6.0–7.6 mL/min/1.73 m², across transport types. Patients receiving 20–24 L met adequacy targets at a GFR range of 4.7–6.5 mL/min/1.73 m².

Ultrafiltration requirements vary with the individual patient, and maintaining euvolemia with an intermittent regimen would require continued intrinsic kidney function, dietary compliance, aggressive use of diuretics, or increased dialysate osmolality. No specific target for peritoneal fluid removal was adopted in the present study: that is, the IPD regimens were not designed with fluid removal being the primary target. The reason for that approach is that patients with significant residual GFR also have significant residual urine output; unfortunately, it is not feasible to quantify residual urine output in a kinetic model in conjunction with residual GFR. Instead, anuric patients were modeled using 1.5% dextrose solutions. As a result, weekly peritoneal fluid removal ranged from 1.3 L to 2.0 L depending on peritoneal transport type and IPD regimen, with the understanding that increased peritoneal UF, which will contribute to solute clearance by increasing convective removal, can be obtained (as clinical conditions require) by using a higher dextrose concentration in exchanges.

Our kinetic modeling predictions for adequate IPD therapy should be compared with previous efforts. First, our estimates of the minimum GFR necessary to achieve weekly clearance targets of approximately

9.7 mL/min/1.73 m² is slightly lower than the original DOQI proposal of 10.5 mL/min/1.73 m² (10). The discrepancy is partly attributable to different assumptions about the relationship between V and BSA, and to the fact that the previous estimate was based on a target weekly Kt/V of 2.0 instead of 1.7. Keshaviah *et al.* used PD Adequest to perform a detailed kinetic analysis for therapy prescriptions similar to that reported here (11). However, their analyses were limited to HA transport patients during continuous ambulatory PD (CAPD) therapy, not to thrice-weekly IPD therapy. Others have reported empiric approaches to the prescription of incremental dialysis using CAPD nighttime dwells based on urea kinetic modeling (12,13). The resulting prescription recommendations were to use one 2.5-L CAPD exchange nightly for a GFR of 8–11 mL/min and two 2.5-L CAPD exchanges nightly for a GFR of 6–8 mL/min. A comparison of those recommendations with ours suggests that incremental dialysis with 10–12 L of IPD therapy thrice-weekly results in weekly clearances similar to those achieved with two 2.5-L CAPD exchanges nightly.

Limitations of the current study design are related mainly to the transport status determinations based on a PET. The PET determinations are typically validated with constant exposure of the peritoneum to dialysate. In IPD regimens, the peritoneum may be “dry” for more than 24 hours, theoretically shifting transport status slightly lower. This brief period of peritoneal rest has recently been shown to improve UF capacity in CAPD patients demonstrating H transport (14), possibly leading to increased fluid and solute removal during IPD. Such a hypothesis would require additional study.

HISTORICAL BACKGROUND OF IPD

In early clinical experiences with PD, patients received PD in a hospital setting on an intermittent schedule. In 1962, Norman Lasker developed the first cyclor device, using glass bottles, tubing with clamps, a solution heater, and a large drain bag (15). With the Lasker cyclor, patients would present to the medical ward and undergo placement of an abdominal catheter, day-long treatments, and removal of the catheter. The process would be repeated on subsequent days. Following the Lasker cyclor, the Physio Control Company (Seattle, WA, USA) combined a reverse-osmosis membrane to create a sterile fluid that was subsequently mixed with a concentrated electrolyte solution and reconstituted into dialysate that was infused into the patient (16). These two cyclor devices allowed for expanded use of IPD in the hospital setting. Permanent silicone rubber catheters were developed by Tenckhoff, providing easier access to the peritoneal cavity, and IPD

regimens expanded to include regimens of up to 4 days weekly in the hospital or at home.

Intermittent PD was practiced around the world, but most experience was centered in Seattle with Henry Tenckhoff's group; in Montpelier, France, with Charles Mion; and in Toronto, Ontario, Canada, with a group at the Toronto Western Hospital led by Dimitrios Oreopoulos (16). In subsequent reviews of this early experience, the investigators acknowledged that, in their opinion, IPD provided adequate dialysis until RKF was significantly lost. However, many practitioners began to understand that, in patients with complete loss of RKF, the intermittent nature of the therapy could not provide adequate long-term dialysis (17). The work described here adds to those early observations on the RKF levels required to improve technique success in IPD.

RECENT CLINICAL EXPERIENCES WITH IPD

In more recent times, IPD has continued to be prescribed in certain clinical settings.

Fourtounas and colleagues described 30 patients managed with hospital-based thrice-weekly IPD (2). In 5 patients, IPD served as a bridge until self-training or spousal assistance could be arranged. Long-term IPD was used in 25 patients. Candidates for the modality had exhausted vascular access or were prior PD patients who could no longer perform home care. Most were anuric. The IPD was performed thrice weekly for 8 – 10 hours, with total dwell volumes per session of 20 – 30 L. The osmolality of the dialysate was chosen to target a UF level of more than 1.5 L per session. The measured Kt/V in this largely anuric population was low, at 1.0 ± 0.26 . Mean survival on in-center IPD was 16.8 months (range: 3 – 43 months) with no symptomatic hyperkalemia, pulmonary edema, or pericarditis. Deaths were largely attributed to cerebral vascular events, sudden death, or respiratory infections. Loss of appetite and vomiting led to 3 patients being transiently hospitalized for additional PD treatments. Two episodes of peritonitis were described (1 episode in 420 patient-months).

The authors considered thrice-weekly IPD to be a viable alternative for patients lacking options for HD or home-based PD. They acknowledged that IPD regimens risk a lower achieved Kt/V, but they noted only minimal uremic symptoms in their experience. Targets for UF were below European best practice guidelines, but the achieved weekly UF on IPD exceeded that in the European Automated Peritoneal Dialysis Outcomes Study of anuric patients on automated PD. The survival rate in their IPD experience suggested that, despite the limitations, IPD could be an option, especially for elderly patients with

advanced comorbidities, smaller muscle mass, RKF, and a controlled diet.

Woywodt and colleagues described a decade-long in-center IPD program in a Hannover hospital (1). This treatment option was covered by German health insurance; assisted PD at home was not. The authors had determined that IPD was the only available option for elderly patients who could not perform PD and who had no vascular access options to allow for HD. The IPD sessions lasted 7.5 – 8 hours using 10 – 15 L dialysate (and up to 20 L, if tolerated). The 30 patients receiving treatment had a mean age of 73 years. Their main comorbidity was congestive heart failure (CHF). The subsequent hospitalization rate was 1.39 admissions per IPD-year, and the peritonitis rate was 1 episode in 48 IPD-months. In patients starting IPD, the median GFR, estimated using the Modification of Diet in Renal Disease equation, was 10 mL/min, suggesting (per our results) that adequate total solute targets were achieved. The mean survival in this IPD cohort was 26.6 months. Surprisingly, 23% of the IPD patients eventually improved, allowing for training and graduation to self-care.

Recent descriptions of IPD in the United States are sporadic and largely anecdotal. A case series describing IPD in the management of late-referred patients requiring an urgent start to PD has been submitted for publication (Ghaffari A. Optimizing PD utilization with urgent start peritoneal dialysis: our experience and review of the literature. Submitted). Patients with newly placed catheters are kept in the recumbent position for low-volume exchanges and are dialyzed in a dialysis center as outpatients on an intermittent schedule based on their degree of uremia. Once the acute uremia has been managed with this IPD regimen, the patients are trained to perform self-care. The same author also noted that, in the overtly uremic patient, initial HD with a temporary vascular access may be required for acute control of symptoms, followed by catheter removal and initiation of IPD. The latter point should be emphasized: Initial HD for acute control of uremia could be combined with IPD to allow for a transition to home therapy with PD and to minimize exposure to the infectious risks of prolonged temporary vascular access.

The foregoing experiences suggest that IPD may still play a role in a select group of dialysis patients who otherwise have limited options. As mentioned, the ideal candidate for IPD would appear to be the newly initiated patient who has yet to be trained, or the patient with advanced comorbidities, small muscle mass, a restricted diet, RKF, and no other options to perform HD or home PD.

Finally, recent reports on in-center thrice-weekly nocturnal HD suggest that nocturnal IPD may be an

alternative delivery strategy (18). Dialysis staff cross-trained in both HD and PD could allow for nocturnal centers that offer both modalities, possibly improving their patient census and economic viability.

Intermittent PD in the home setting has also been described (19,20). In the home setting, IPD using automated PD 3 or 4 times weekly has been described as a method of initiating dialysis as an incremental regimen.

ADDRESSING SPECIFIC CLINICAL SCENARIOS WITH IPD

Intermittent PD has been described for the management of PD patients undergoing hernia repair. Bargman's group in Toronto published a protocol used for perioperative management of 50 consecutive patients undergoing hernia repair without the use of interim HD (21). Beginning 48 hours postoperatively, patients are initiated on IPD in the recumbent position for 2 weeks if on CAPD and for 1 week if APD; they are then graduated to slowly increasing PD regimens. The IPD delivered 10 exchanges of 1 L each over 10 hours. Mean renal creatinine clearance values were 4.5 mL/min, and 9 patients were anuric. No patients developed hyperkalemia, leakage, wound dehiscence, or immediate hernia recurrence, and the authors recommend this approach for hernia repair in patients on PD therapy.

In-center IPD has been described for the management of severe refractory CHF even in patients with significant RKF (22). In elderly populations, CHF remains the leading cause of hospitalization, and patients who become refractory or intolerant to diuretics are often initiated on dialysis for control of extracellular fluid despite significant RKF (23,24). Intermittent PD to achieve UF has been documented to improve symptoms, reduce hospitalization, and improve cardiorenal physiology, allowing for continuation of protective medications such as angiotensin converting-enzyme inhibitors or spironolactone. A recent report from Spain described the significant impact of peritoneal UF on the CHF-related hospitalization rate, the mortality rate, and quality of life (25). Japanese investigators described a thrice-weekly IPD regimen for the control of refractory CHF in elderly patients with advanced chronic kidney disease (26).

CONCLUSIONS

Kinetic modeling of small-solute clearance during thrice-weekly IPD has demonstrated the GFR necessary to achieve current urea clearance targets. In selected patients in whom fluid balance can be maintained, IPD therapy can serve as a bridge until home training or assistance can be arranged, or as a method of managing

the longer-term patient who has lost vascular access or can no longer perform self-care. During the postoperative period, IPD has been used until full-dose PD can be resumed, and it may be valuable in the management of severe CHF by providing intermittent UF that favorably affects aberrant cardiorenal physiology. Revisiting this older PD regimen suggests that IPD can provide adequate urea clearance targets in patients with significant remaining RKF and may allow for an incremental treatment strategy in selected patients.

DISCLOSURES

Authors SG, AA, JS, and JKL are employees of Baxter Healthcare Corporation.

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