ICODEXTRIN SIMPLIFIES PD THERAPY BY EQUALIZING UF AND SODIUM REMOVAL AMONG PATIENT TRANSPORT TYPES DURING LONG DWELLS: A MODELING STUDY

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◆ **Background:** In recent years, results from clinical studies have changed the focus of peritoneal dialysis (PD) adequacy from small solute clearance to volume control, resulting in continued efforts to improve fluid and sodium removal in PD patients. We used a modified 3-pore model to theoretically predict fluid and solute removal using glucose-based and icodextrin solutions for a wide range of transport characteristics with automated PD (APD) and continuous ambulatory PD (CAPD) therapies.

◆ **Methods:** Simulations were performed for the day (APD: 15-hr, 2.27% glucose and 7.5% icodextrin; CAPD: 3x5-hr, 1.36% and 2.27% glucose) and night (APD: 9-hr, 1.36% glucose; CAPD: 9-hr, 2.27% glucose and 7.5% icodextrin) dialysis periods separately. During APD, the number of night exchanges (N) was varied from 3 to 7. Ultrafiltration (UF), sodium removal (NaR), total carbohydrate absorption (CHO), UF efficiency (UFE), and sodium removal efficiency (NaRE) were calculated. Typical patients in fast (i.e. high, H), average (high-average, HA; low-average, LA), and slow (low, L) transport groups with no residual kidney function were considered.

◆ **Results:** The effective dwell times varied between 1.0 and 14.7 hours depending on the number of exchanges. With glucose-based solutions, differences in UF and NaR between H and L transport patients ranged from 140 mL and 2 mmol (APD night, n = 7) to 778 mL and 56.4 mmol (CAPD day, 2.27%). With icodextrin, differences in UF and NaR ranged from 1 mL and 1.1 mmol (CAPD night) to 59 mL and 6.1 mmol (APD day). The use of icodextrin resulted in greater CHO than 2.27% glucose (APD: 27.1 – 35.6 g more; CAPD: 17.1 – 17.5 g more). The UFE and NaRE were greater for all patients with icodextrin than with glucose-based solution in both therapy modalities, except for slow transport patients in CAPD.

◆ **Conclusion:** This modeling study shows that the dependence of UF and NaR on patient transport type observed with

glucose-based solutions can be minimized using icodextrin during the long dwells of APD and CAPD. While this approach simplifies the PD prescription by minimizing the dependencies of ultrafiltration and sodium removal on patient transport type when using icodextrin, it improves fluid and sodium removal efficiencies in fast and average transport patients without any added glucose exposure.

Perit Dial Int 2016; 36(1):79–84 epub ahead of print: 02 Sept 2014
<http://dx.doi.org/10.3747/pdi.2013.00081>

KEY WORDS: Ultrafiltration; sodium removal; ultrafiltration efficiency; sodium removal efficiency; icodextrin; APD; CAPD.

The importance of fluid and sodium removal in the management of peritoneal dialysis (PD) patients is well recognized (1,2) and is challenging in patients with fast membrane transport characteristics (3). Inadequate removal of fluid and sodium has been shown to increase the risk of overhydration and hypertension (4). Given the high prevalence of cardiovascular disease, recent guidelines have emphasized the importance of maintaining euvolemia in the PD patient population (5), and new therapy modalities and novel PD solutions have been proposed to overcome these difficulties (6–8).

Fast transport patients, unable to achieve sufficient fluid removal on continuous ambulatory PD (CAPD), have been recommended to use an automated device delivering short nighttime exchanges to achieve improved ultrafiltration (UF) volumes and icodextrin, a 7.5% glucose-polymer PD solution (Baxter Healthcare Corporation, Deerfield, IL, USA), during the long daytime dwell. The strongest support of this recommendation was reported recently by Johnson *et al.* who demonstrated a significant survival advantage of automated PD (APD) compared with CAPD in fast transport patients from a large number of dialysis centers in Australia and New Zealand (9). The use of icodextrin was not, however, part of the collected data from that study and specific UF volumes and sodium removal

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Received 29 April 2014; accepted 8 May 2014.

were not reported (9). As a result, it was not possible to elaborate on the role that icodextrin may have played in the demonstrated survival advantage and any potential improvements in fluid and solute removal.

Early studies of icodextrin as a long dwell PD solution evaluated its metabolism, safety profile, and dialysis adequacy relative to glucose-based PD solutions (10–13). In several studies, sodium removal with icodextrin was reported only for the study population as a whole (14–17) and the dependence of UF on patient transport characteristics was discussed in a limited number of cases (18,19). In the present study, we used the 3-pore model to address these data gaps and illustrate the potential simplification and optimization of the dialysis prescription across patient transport groups when using icodextrin.

METHODS

PATIENT DATA

Patient parameters were obtained from data submitted to Baxter Healthcare Corporation's Renal Division by centers around the United States and Canada participating in a national adequacy initiative program (data on file from TARGET, Treatment Adequacy Review for Gaining Enhanced Therapy, Baxter Healthcare Corporation, Deerfield, IL, USA). As previously described in several similar modeling studies (20,21), the data were first grouped in 4 peritoneal equilibration test (PET) categories (high: H, high-average: HA, low-average: LA, low: L) according to 4-hour dialysate/plasma (D/P) creatinine measurements (22). To be consistent with the nature of solute transport across the peritoneal membrane, we will refer to these groups in this report as fast (H), average (HA and LA) and slow (L) peritoneal transport groups, unless specific reference to 1 of the 4 PET categories is needed. Based on the combination of a long overnight dwell and 4-hour PET results, kinetic parameters such as the solute mass transfer area coefficient (MTAC, mL/min), ultrafiltration coefficient (LPA, mL/min/mmHg), and transport surface area (or unrestricted pore area over diffusion distance) (A_0/dX , cm) were estimated using PD Adequest 2.0 (23). As a last step, 4 average patients were created as representatives of each category in small, medium, and large body surface area (BSA) groups. Relevant kinetic parameters for typical patients with BSA between 1.7 and 2.0 m² were considered as shown in Table 1.

COMPUTER MODEL

A modified 3-pore model of peritoneal transport based on PD Adequest 2.0 was used. The Matlab (version

7.7.0.471, Mathworks Inc., Massachusetts, USA) software program was used to integrate the model equations numerically. Steady-state plasma concentrations of icodextrin metabolites were incorporated to consider patients who routinely use icodextrin (data on file, Baxter Healthcare Corporation). PD Adequest 2.0 was validated for UF and small solute transport (23,24) and this modified kinetic model was previously used to predict icodextrin absorption (25) and sodium removal (6,20).

SIMULATED THERAPY CONDITIONS

Simulations were performed for the daytime (APD: 15-hour dwell, 2.27% glucose and 7.5% icodextrin; CAPD: 3x5-hour cycles, 1.36% and 2.27% glucose) and nighttime (APD: 9-hr, 1.36% glucose; CAPD: 9-hr, 2.27% glucose and 7.5% icodextrin) dialysis periods separately. A fill volume (VF) of 2 L and peritoneal residual volume of 350 mL were assumed in all cases. During APD, the number of night exchanges (N) was varied from 3 to 7. Ultrafiltration, sodium removal (NaR), total carbohydrate absorption (CHO), UF efficiency (UFE) defined as UF per CHO (mL/g), and sodium removal efficiency (NaRE), defined as sodium removed per CHO (mmol/g)

TABLE 1
Peritoneal Equilibration Test Data and Kinetic
Parameters Representing Typical High,
High Average, Low Average, and
Low Transport Patients

	H	HA	LA	L
4-hr D/P	0.86	0.71	0.59	0.43
4-hr D/D0	0.25	0.34	0.44	0.53
BSA, m ²	1.84	1.86	1.87	1.85
TBW, L	40.64	41.28	42.32	40.59
Glucose MTAC, mL/min	16.34	11.71	8.35	5.96
Urea MTAC, mL/min	27.71	23.14	18.40	15.92
Ico MW 1 MTAC, mL/min	6.39	4.97	4.01	3.30
Ico MW 2 MTAC, mL/min	3.57	2.92	2.48	2.16
Ico MW 3 MTAC, mL/min	1.89	1.70	1.57	1.48
Ico MW 4 MTAC, mL/min	1.29	1.27	1.25	1.24
Ico MW 5 MTAC, mL/min	1.20	1.20	1.20	1.20
LPA, mL/min/mmHg	0.0575	0.0560	0.0563	0.0554
A_0/dX , cm	40,398	29,362	21,942	16,402

H = High; HA = High Average; LA = Low Average; L = Low; D/P = dialysate/plasma; D/D0 = dialysate glucose; BSA = body surface area; TBW = total body water; MTAC = mass transfer area coefficient; Ico MW 1–5 = simulated icodextrin molecular weight fractions; LPA = ultrafiltration coefficient; A_0/dX = transport surface area.

were calculated. A summary of the simulated conditions is shown in Table 2.

RESULTS

The simulated effective dwell time (i.e. total dwell time adjusted for peritoneal transport during filling and draining the dialysis fluid as described elsewhere [26]) varied between 1.0 and 14.7 hours depending on the number of exchanges.

Predicted UF, NaR, and CHO with icodextrin and 2.27% glucose solutions during the long dwells of APD and CAPD are shown in Table 3. The largest differences in UF and NaR with icodextrin occurred in fast transporters in both therapy modalities. Unlike glucose, icodextrin resulted

in minimal differences among transport types. The total CHO was greater when using icodextrin in all transport types, which was primarily due to larger infused icodextrin mass. As shown in Table 4, the effect of increasing beyond 5 APD night exchanges was minimal across all transport types and was more pronounced for NaR than UF. Fast-to-average transport patients (H and HA) on CAPD achieved no net UF and NaR with 1.5% glucose solution.

As shown in Table 5, the UFE was greater with icodextrin except for slow transport patients (L) on CAPD. Differences in UFE among transport types were greater with glucose solutions than with icodextrin. The trend of NaRE followed that of UFE across transport types and therapy modalities. The negative values of UFE and NaRE denote fluid or sodium absorption from the peritoneal cavity as opposed to net (positive) ultrafiltration.

DISCUSSION

Current predictions demonstrate that the wide ranges of UF and sodium removal that exist among patients using glucose-based solutions during long dwells can be minimized using icodextrin with improvements that are more pronounced with APD than CAPD. They also demonstrate diminished variations in UF and sodium removal among patients with increasing numbers of exchanges. When combined, these features reveal that APD and CAPD regimens using icodextrin are simplified as they provide comparable UF and sodium removal across different patient transport types.

These predicted improvements with icodextrin have been clinically observed in studies comparing dialysis adequacy in patients undergoing CAPD and APD (15,27).

TABLE 2
Summary of Simulated Therapy Conditions for the Day and Night Periods of APD and CAPD

	APD		CAPD	
	Day	Night	Day	Night
T, hours	15	9	15	9
N	1	3 / 5 / 7	3	1
VF	2L	2L	2L	2L
PD Solution	2.27% G ICO	1.36% G	1.36, 2.27% G	2.27 G ICO

APD = automated peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis; T = total exchange time; N = number of exchanges; VF = fill volume; G = glucose; PD = peritoneal dialysis; ICO = icodextrin.

TABLE 3
Summary of Simulated Therapy Conditions for the Long Dwell Periods of APD and CAPD

	UF (mL)		NaR (mmol)		CHO (g)	
	ICO	2.27% G	ICO	2.27% G	ICO	2.27% G
APD						
H	465	-416	70.1	-48.5	78.9	43.3
HA	488	-291	72.3	-33.4	73.6	43.0
LA	501	-135	72.9	-15.9	69.5	41.7
L	524	71	76.1	4.4	66.2	39.1
CAPD						
H	388	-108	59.1	-9.8	59.3	42.2
HA	386	13	58.1	2.0	55.4	40.5
LA	382	147	56.7	13.9	52.5	37.1
L	389	299	58.0	26.8	50.2	32.7

UF = ultrafiltration; NaR = sodium removed; CHO = carbohydrate absorbed; ICO = icodextrin; G = glucose; APD = automated peritoneal dialysis; H = high; HA = high-average; LA = low-average; L = low; CAPD = continuous ambulatory peritoneal dialysis.

TABLE 4
Summary of Simulated Therapy Conditions for the Short Dwell Periods of APD and CAPD

	APD									CAPD					
	UF (mL)			NaR (mmol)			CHO (g)			UF (mL)		NaR (mmol)		CHO (g)	
	N=3	N=5	N=7	N=3	N=5	N=7	N=3	N=5	N=7	1.36%	2.27%	1.36%	2.27%	1.36%	2.27%
H	20	168	246	4.5	20.0	27.8	57.4	74.5	83.3	-223	262	-21.2	31.9	67.5	114.9
HA	103	230	287	9.1	21.6	27.3	49.5	61.1	66.4	-75	520	-10.2	51.2	61.5	103.1
LA	171	276	316	12.6	22.3	26.4	40.8	48.4	51.4	61	771	-0.6	68.5	53.3	87.6
L	266	357	386	18.8	26.9	29.8	33.2	38.0	39.7	233	1040	11.9	88.4	44.9	71.8

APD = automated peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis; UF = ultrafiltration; NaR = sodium removed; CHO = carbohydrate absorbed; N = number of exchanges; H = high; HA = high-average; LA = low-average; L = low.

TABLE 5
Summary of Ultrafiltration and Sodium Removal Efficiencies for APD and CAPD

	APD Day				APD Night				CAPD Day				CAPD Night			
	2.27%		ICO		N=3		N=7		1.36%		2.27%		2.27%		ICO	
	UFE	NaRE	UFE	NaRE	UFE	NaRE	UFE	NaRE	UFE	NaRE	UFE	NaRE	UFE	NaRE	UFE	NaRE
H	-9.6	-1.1	5.9	0.9	0.3	0.1	3.0	0.3	-3.3	-0.3	2.3	0.3	-2.6	-0.2	6.6	1.0
HA	-6.8	-0.8	6.6	1.0	2.1	0.2	4.3	0.4	-1.2	-0.2	5.0	0.5	0.3	0.0	7.0	1.0
LA	-3.2	-0.4	7.2	1.0	4.2	0.3	6.2	0.5	1.1	0.0	8.8	0.8	4.0	0.4	7.3	1.1
L	1.8	0.1	7.9	1.2	8.0	0.6	9.7	0.7	5.2	0.3	14.5	1.2	9.1	0.8	7.8	1.2

APD = automated peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis; ICO = icodextrin; N = number of exchanges; UFE = ultrafiltration efficiency (mL/g); NaRE = sodium removal efficiency (mmol/g); H = high; HA = high-average; LA = low-average; L = low.

Specifically, equivalent UF was shown using icodextrin compared with glucose-based solutions across all transport types due to significant UF improvements in fast and average transport patients during CAPD (19) and APD (28). In a recent report, Davison *et al.* demonstrated that the fundamental limitations of APD, such as sodium sieving, can be overcome by properly adjusting the number of night exchanges according to the patients' membrane transport characteristics and using icodextrin during the long day exchange (27).

These latter clinical observations are consistent with our predictions suggesting that the frequently observed low removal of sodium in APD compared with CAPD patients may also result from poor UF during the long day dwell, in addition to sodium sieving during the short exchanges of APD (17,29). Namely, it is not uncommon for fast transport patients using glucose-based solutions to complete the long day dwell with zero or negative net fluid removal (10–12), and hence, sodium removal. Such fast transport patients with high D/P creatinine were reported to have lower convective sodium mass transport associated with reduced transcapillary ultrafiltration, while demonstrating significantly greater convective sodium

mass transport associated with fluid absorption when compared to patients with low D/P creatinine (30).

It is evident that UF and NaR efficiency improvements obtained with icodextrin in fast transport patients are primarily due to increased UF and NaR rather than decreased CHO. Despite its lower percent absorption, the large icodextrin mass present in the 2 L, 7.5% icodextrin solution (i.e. 150 g of icodextrin vs 45.4 g of glucose in 2.27% glucose solution) results in greater total carbohydrate absorption during the long dwells across all transport types. Garcia-Lopez *et al.* showed that 39% (58.5 g) of instilled icodextrin was absorbed during 10- to 16-hour dwells producing 589 mL of UF, resulting in UF efficiency of 10.1 mL/g (31). Plum *et al.* found an average UF of 278 mL and icodextrin absorption of 33% (49.5 g) resulting in UF efficiency of 5.6 mL/g during long APD dwells of 13.4 hours on average (12). These findings are consistent with our predictions. While the trend of NaR efficiency is expected to follow that of the UF efficiency based on the current study, no specific data on NaR efficiency has been published to date for comparison.

Our study has several limitations. First, the modeled patients were assumed to have no residual kidney

function and urine volume. While this was necessary to compare only the effects of the parameters of interest (i.e. solution type, therapy modality, and dwell time), estimates of total (i.e. peritoneal + residual) 24-hour UF and NaR were not possible. This is likely a concern for patients new to dialysis. Second, the modeled patients were differentiated primarily with respect to the membrane characteristics relating to small solute transport (i.e. 4-hour D/P creatinine). Although this allowed us to evaluate the majority of the PD patient population, wider parameter ranges and more specific cases need to be investigated to address removal of larger molecules, patients with varying degrees of BSA, and total fluid absorption (from the peritoneal cavity). Third, our predictions assumed a single value of blood sodium concentration (137 mmol/L). Therefore, it is likely that patients with varying blood sodium concentrations will achieve UF and sodium removal different from those presented in this report. Based on an independent analysis, we predicted that serum sodium variations up to ± 3 mmol/L would result in ± 20 mL differences in UF and ± 4.5 mmol differences in sodium removal during a long APD dwell in fast transport patients. Fourth, we differentiated APD and CAPD therapies only based on dwell times and number of exchanges; all other underlying patient properties were assumed to be the same. For instance, it is likely that APD patients with larger peritoneal residual volume achieve less UF during the long dwell than CAPD patients when using icodextrin (32). It is also possible that variations in plasma albumin and intra-abdominal pressure due to supine and sitting positions could alter ultrafiltration. Fifth, and perhaps most important, the predictions in this study are only as accurate as the models used. The models we used herein are based on the 3-pore model, the current paradigm for modeling peritoneal fluid and solute transport; nonetheless, these models are simplified representations of the physiological processes occurring during PD. Although modeling of ultrafiltration when using icodextrin may still have some limitations, the model we have used herein is the most sophisticated to date (25). To that end, one characteristic feature of our application of the 3-pore model is the lack of difference in fluid transport parameters (i.e. LPA) among the patient types. This assumes that the difference in glucose absorption from the peritoneal cavity is essentially the only factor responsible for the difference in UF when glucose is the osmotic solute. The difference in absorption of icodextrin, although present, is relatively small and has a lower effect on UF, which equalizes UF and sodium removal across patient types. This lack of difference in LPA observed with our model using a large patient data set is a new confirmation of previous

direct evidence that demonstrated that fluid transport parameters including LPA and osmotic conductance for glucose, which is proportional to LPA, do not depend on the patient type or, equivalently, do not correlate with D/P creatinine (33–35). Finally, it was not possible for us to compare the predicted NaRE with actual clinical data, emphasizing the need to consider this increasingly important parameter in future clinical studies.

CONCLUSIONS

We performed a modeling study to compare the effects of icodextrin and glucose-based solutions on ultrafiltration and sodium removal in APD and CAPD therapies for a wide range of transport characteristics. Our results demonstrated that PD therapies can be optimized and simplified, i.e. the dependencies of ultrafiltration and sodium removal on membrane transport type are minimized, when using icodextrin. Ultrafiltration volume and sodium removal efficiencies were also improved with icodextrin primarily during the long dwell of APD due to sustained UF as opposed to decreased CHO.

DISCLOSURES

The authors are employees of Baxter Healthcare Corporation and have ownership interests.

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