PERITONEAL RESIDUAL VOLUME INDUCES VARIABILITY OF ULTRAFILTRATION WITH ICODEXTRIN

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◆ **Background:** Icodextrin induces ultrafiltration (UF) during long-dwell exchanges by creating a difference in oncotic pressure between the peritoneal cavity and plasma; however, the mechanisms governing intra-patient and inter-patient variability in UF when icodextrin is used remain largely unexplained. In the present study, we show theoretically that differences in peritoneal residual volume (V_R) have a more profound effect on UF with icodextrin use than with glucose use. This phenomenon is attributed to a differential effect of V_R on oncotic, rather than osmotic, pressure between the peritoneal cavity and plasma.

◆ **Methods:** The three-pore model was used to calculate the effect on UF of V_R between 150 mL and 1200 mL when 7.5% icodextrin (ICO) or 3.86% glucose solution is used at the end of a 12-hour dwell in the four patient transport groups (that is, fast to slow). Oncotic (with ICO) and osmotic (with glucose) pressure differences averaged over the entire dwell were also calculated.

◆ **Results:** As expected, at a nominal V_R of 300 mL, UF with glucose differed substantially between the four patient transport groups (2 – 804 mL), whereas UF with ICO did not (556 – 573 mL). When V_R was increased to 1200 mL from 150 mL, the concentrations of the oncotic and osmotic agents at the start of the dwell with an infusion volume of 2 L decreased to 4.9% from 7.0% with ICO and to 2.5% from 3.6% with glucose. The decrease in UF on average was greater with ICO [to 252 mL from 624 mL: that is, a reduction of 372 mL (60%)] than with glucose [to 292 mL from 398 mL: that is, a reduction of 106 mL (27%)]. Those trends agreed with the calculated reductions in the oncotic pressure difference with ICO [reduction of 12 mmHg (49%)] and the osmotic pressure difference with glucose [reduction of 19 mmHg (33%)].

◆ **Conclusions:** When ICO is used, V_R modifies the oncotic pressure difference between the peritoneal cavity and

plasma to substantially alter UF. This modification suggests that potential causes of increased V_R should be considered when UF with ICO is considerably less than expected. Prospective clinical studies evaluating the relationship between V_R and UF with ICO are warranted to validate the theoretical predictions in this report.

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A review of clinical studies that measured ultrafiltration (UF) with icodextrin (1–18), a 7.5% glucose polymer long-dwell peritoneal dialysis (PD) solution (Baxter Healthcare Corporation, Deerfield, IL, USA), reveals considerable variability, with UF ranging from 204 mL to 950 mL on average. Specific accounts of such variability were previously reported (11,19), and possible sources were described (20,21).

Although the variability in UF seems random as a whole, trends were observed when specific groups of patients were analyzed. For example, larger UF volumes have been shown in patients new to PD (20), in men compared with women, in fast compared with slow peritoneal transporters (11), in diabetic compared with nondiabetic patients (8,11), and in patients on continuous ambulatory PD (CAPD) compared with those on automated PD (APD) (17). Most interestingly, a recent study demonstrated that UF with icodextrin in APD patients performing an additional daytime exchange (9-hour icodextrin dwell + 6-hour glucose dwell) was less on average than that in CAPD patients (9-hour icodextrin dwell only), even though the icodextrin dwell times were similar (22).

To date, an increased peritoneal residual volume (V_R) has been shown to lower UF with glucose-based PD solutions (23); however, an increased V_R has not

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been considered a contributing factor to UF variability with icodextrin. In this report, we show theoretically that V_R has a more pronounced effect on UF with the use of icodextrin than with the use of glucose-based PD solutions.

METHODS

Ultrafiltration was simulated using a modified three-pore model based on PD Adequest 2.0 (Baxter Healthcare Corporation) (14,24) with the use of 3.86% glucose and 7.5% icodextrin solutions during a 12-hour dwell in average-sized patients having high (or fast), high-average, low-average, and low (or slow) transport characteristics. Peritoneal V_R was systematically varied from 150 mL to 1200 mL, representing the range previously reported (25).

The effect of V_R on solution concentrations and the resulting percentage dilution of osmotic (glucose) and oncotic (ICO) agents immediately after infusion was approximated by the equations

$$C_D = (C_R \cdot V_R + C_I \cdot V_I) / (V_I + V_R) \text{ and} \quad [1]$$

$$\text{Dilution} = (C_I - C_D) / C_I \cdot 100, \quad [2]$$

where C_D is the dialysate concentration after infusion, C_R is the concentration in V_R , C_I is the infused concentration, and V_I is the infused ("fill") volume. For this approximation, the icodextrin concentration in V_R immediately preceding the icodextrin dwell under consideration was assumed to be in equilibrium with blood because of continuous draining and dilution of icodextrin remaining from the preceding long day dwell by multiple night exchanges using glucose-based dialysis fluids. The glucose concentration in V_R was also assumed to be equal to that in blood (0.1 g/dL or 6 mmol/L).

Calculation of dialysate osmolality was based on the concentrations of solutes present (glucose, sodium, calcium, magnesium, chloride, lactate, bicarbonate, urea, and creatinine). At the start of the dwell, osmolality varied as a function of infused solution volume (osmolality, O_I : 483 mOsmol/L for 3.86% glucose) and V_R (osmolality, O_{VR} : assumed equal to plasma osmolality, 300 mOsmol/L) as shown in the equation

$$O_{D0} = (O_I \cdot V_I + O_{VR} \cdot V_R) / (V_I + V_R), \quad [3]$$

where O_{D0} is the dialysate osmolality immediately after infusion.

At the end of the 12-hour dwell, complete equilibration with plasma was assumed for all solutes considered except glucose and ICO, whose concentrations were calculated on the basis of specific absorption characteristics derived from previous measurements in APD patients

(15). Osmolality was calculated as the sum of the solute concentrations (in mmol/L):

$$O_{D,END} = \sum C_{D,END}, \quad [4]$$

where $O_{D,END}$ is the dialysate osmolality, and $C_{D,END}$ is the solute concentration at the end of the dwell.

Finally, the equations

$$\Delta OSM = \sigma_G \cdot (O_p - O_D) \cdot 19.3 \text{ mmHg and} \quad [5]$$

$$\Delta ONC = (0.38 \cdot SA + 7.72) - 0.88 \cdot C_{D,ICO} \text{ mmHg} \quad [6]$$

were used to calculate the average osmotic and oncotic pressure differences (that is, the arithmetic mean of the values at the start and end of the dwell: ΔOSM and ΔONC) between plasma and dialysate contributing to UF over the entire dwell time (26), where O_p (300 mOsmol/L) is plasma osmolality (27), σ_G (0.03) is the assumed reflection coefficient of glucose (28), and SA (40 g/L) is the serum albumin concentration. The dialysate concentration of icodextrin ($C_{D,ICO}$ in equation 6) was either calculated using equation 1 (at the start of the dwell) or derived from previous measurements (15) (at the end of the dwell). Differences in small-solute concentrations were assumed not to contribute to UF with icodextrin.

RESULTS

At a nominal V_R of 300 mL, UF with glucose differed substantially between the transport groups, but UF with icodextrin did not (Table 1). When V_R was increased to 1200 mL from 150 mL, with $V_I = 2$ L, the concentrations of oncotic agents at the start of the dwell decreased to 2.45% from 3.60% with glucose (6.8% – 36.4% dilution) and to 4.91% from 7.02% with icodextrin (6.4% – 34.5% dilution; Table 2). At the end of a 12-hour dwell, approximately 77% of the glucose (59.4 g) and 32% of the icodextrin (48 g) were absorbed, similar to values determined from direct measurements (15).

As shown in Table 3, increasing the V_R to 1200 mL from 150 mL resulted in a greater decrease in ΔONC than in ΔOSM . At the beginning of the dwell, ΔOSM varied from

TABLE 1
Ultrafiltration During a 12-Hour Dwell with a
Peritoneal Residual Volume of 300 mL

Peritoneal solution	Ultrafiltration (mL) by membrane type			
	High (fast)	High average	Low average	Low (slow)
3.86% Glucose	2	225	496	804
7.5% Icodextrin	556	562	563	573

TABLE 2

Dialysate Concentrations and Dilutions of Glucose and Icodextrin as a Function of Peritoneal Residual Volume^a

V_R (mL)	Concentration (%) of		Dilution (%) of	
	Icodextrin	Glucose	Icodextrin	Glucose
150	7.02	3.60	6.4	6.8
300	6.60	3.37	12.0	12.7
450	6.23	3.17	16.9	17.8
600	5.91	2.99	21.2	22.4
750	5.62	2.84	25.1	26.5
900	5.36	2.70	28.6	30.2
1050	5.12	2.57	31.7	33.4
1200	4.91	2.45	34.5	36.4

^a Icodextrin and glucose concentrations in the V_R were assumed to be equal to those in blood.

TABLE 3

Estimated Calculated Osmotic (OSM) and Oncotic (ONC) Pressure Differences at the Beginning and End of a 12-Hour Dwell with Glucose or Icodextrin, by Residual Volume (V_R)^a

Time (hours)	V_R (mL)	Glucose			Icodextrin		
		(%)	(g)	Δ OSM (mmHg)	(%)	(g)	Δ ONC (mmHg)
0	150	3.60	77.4	-98	7.0	150.9	-39
	1200	2.45	78.5	-66	4.9	157.2	-20
12	150	0.70	17.8	-17	3.7	102.6	-10
	1200	0.52	18.1	-11	3.1	106.9	-4

^a Icodextrin and glucose concentrations in the V_R were assumed to be equal to those in blood.

-98 mmHg to -66 mmHg with glucose, and Δ ONC varied from -39 mmHg to -20 mmHg with icodextrin. That trend was maintained at the end of the dwell (Table 3). When averaged over the duration of the 12-hour dwell (that is, taken as a mean), Δ OSM ranged from -57 mmHg to -38 mmHg (33% reduction), and Δ ONC ranged from -24 mmHg to -12 mmHg (49% reduction; Table 4). As a comparison, at a fixed V_R of 150 mL, ± 15 g/L variability in the concentration of serum albumin (that is, 40 ± 15 g/L) caused variability of ± 6 mmHg [that is, -24 ± 6 mmHg ($\pm 25\%$)] in the mean Δ ONC.

For both oncotic agents, Figure 1 shows the dependence of UF on V_R when averaged over all patients. The reduction in UF with a larger V_R was more substantial with icodextrin than with glucose in all individual patient groups (data not shown). With glucose, UF declined to

TABLE 4

Time-Averaged Osmotic (OSM) and Oncotic (ONC) Pressure Differences and Corresponding Reductions, by Residual Volume (V_R)^a

Variable	V_R (mL)	Glucose Δ OSM (mmHg)	Icodextrin Δ ONC (mmHg)
Average (0–12 h)	150	-57	-24
	1200	-38	-12
Reduction (%)		33	49

^a Icodextrin and glucose concentrations in the V_R were assumed to be equal to those in blood.

Figure 1 — (A) Ultrafiltration (UF) as a function of residual volume (V_R). Solid line: glucose. Dashed line: icodextrin. (B) Reductions in UF and corresponding osmotic pressure difference (Δ OSM) and oncotic pressure difference (Δ ONC) with glucose and icodextrin when V_R was increased to 1200 mL from 150 mL.

292 mL from 398 mL [a reduction of 106 mL (27%)], and with icodextrin, it declined to 252 mL from 624 mL [a reduction of 372 mL (60%)] when V_R was increased to 1200 mL from 150 mL [Figure 1(A)]. Reductions in UF agreed with the corresponding reductions in osmotic and oncotic pressure differences [Figure 1(B)].

DISCUSSION AND CONCLUSIONS

Ultrafiltration with icodextrin is attributable to sustained oncotic pressure differences exerted primarily between albumin in plasma and glucose polymers in dialysate, as has been well established (1,26,29). Based on a detailed analysis of UF in APD patients (11), Venturoli *et al.* (21) recently suggested that plasma oncotic pressure was the primary factor governing the variability of UF-versus-time curves with icodextrin. Nevertheless, although they noted some variability in serum albumin levels, no clear relationship to UF variability was established (21).

The present report suggests a previously unexplored clinically relevant factor: that is, the variability in V_R from the preceding exchange, which can in part explain the observed variability in UF when icodextrin solution is used. In this regard, our work confirms the theoretical arguments previously offered by Venturoli *et al.* (21) that the variability in oncotic pressure differences, likely caused by the combined variability in V_R and serum albumin concentration, largely determine the variability in UF with icodextrin. Our calculations demonstrate that a reduced icodextrin concentration (4.9%) caused by a large V_R results in considerably less UF, which is consistent with predictions by Rippe and Levin (20), who showed that 4.0% icodextrin results in minimal UF. Interestingly, our calculations also demonstrate that the effect of V_R is not as substantial when a glucose-based PD solution is used.

Considering the studies that reported less UF with icodextrin in APD than in CAPD (17,22), the results from the present theoretical analysis are strikingly consistent with the mechanics of drain during the night exchanges of APD when the patient is supine, the drain line is most susceptible to kinks, and the cyclor is programmed to advance to the next exchange when the drain flow rate falls below a preset threshold, all of which may lead to a larger than normal V_R and contribute to the presumed variability in UF. In a recent study, Davis *et al.* (30) reported that insufficient drain was associated with 88% of the increased intraperitoneal volume cases they analyzed. Their finding suggests that potential causes of increased V_R should be explored by the attending clinical team in situations in which UF with icodextrin is considerably less than predicted.

The results of the present study may have significant clinical implications. For example, they suggest that icodextrin may yield higher UF volumes in APD patients who perform a self-drain at the conclusion of their night exchanges before the infusion of icodextrin solution. A self-drain is similar to a CAPD exchange, in that the

patient performs the drain in a sitting position, permitting more complete drain of peritoneal effluent (31) and possibly a smaller, less variable V_R . Unfortunately, a direct confirmatory comparison of UF with icodextrin in APD and CAPD patients is difficult to achieve because of differences in dwell times, which are typically 8–10 hours in CAPD and 12–16 hours in APD. To that extent, the study by Yu *et al.* (22) provides important new information.

Further prospective clinical studies evaluating the relationship between V_R and UF with icodextrin are warranted to validate the theoretical predictions in this report.

DISCLOSURES

The authors are employees of Baxter Healthcare Corporation.

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