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Augmenting solute clearance in peritoneal dialysis

RAYMOND T. KREDIET, CAROLINE E. DOUMA, RUDOLF W. VAN OLDEN, MARJA M. HO-DAC-PANNEKEET, and DIRK G. STRUIJK

Renal Unit, Department of Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

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Background. The removal of low molecular weight solutes by peritoneal dialysis is less than by hemodialysis. The targets for Kt/V_{urea} and creatinine clearance formulated in the Dialysis Outcome Quality Initiative are unlikely to be achieved in a substantial portion of peritoneal dialysis patients. Possibilities to increase small solute clearances have therefore been subject to many investigations.

Methods. A review of the literature and of recent new data on determinants of solute removal, such as residual renal function, the role of drained dialysate volume and manipulation of the diffusive capacity of the peritoneum are presented.

Results. The contribution of residual GFR is more important for the clearance of creatinine than for Kt/V_{urea}. It is even more important for the removal of organic acids that are removed from the body by tubular secretion. High dosages of furosemide increase the urinary volume and the fractional Na^+ excretion, but have no effect on the magnitude of residual GFR, renal creatinine clearance, renal urea clearance, and peritoneal transport characteristics. The drained dialysate volume per day is the main determinant of the peritoneal removal of urea. Its effect decreases the higher the molecular weight of a solute. It can be augmented by using large instillation volumes, by the application of more exchanges, and by increasing peritoneal ultrafiltration. A large exchange volume is especially effective in patients with an average transport state, but in those with high solute transport rates, Kt/V_{urea} is especially influenced by the number of exchanges. Possibilities to increase ultrafiltration are discussed. The diffusive capacity of the peritoneum can be augmented by using low dosages of intraperitoneally administered nitroprusside. This increases solute transport most markedly when it is applied in combination with icodextrin as osmotic agent.

Conclusions. Small solutes clearances cannot be increased by furosemide. Increasing the instilled volume of dialysis fluid and the number of exchanges both affect solute clearance. Studies are necessary on long-term effects of manipulation of the peritoneal membrane with nitroprusside.

The objective of peritoneal dialysis is to remove uremic toxins and excess fluid from the body; however, this goal is not achieved by intermittent peritoneal dialysis (IPD) in the majority of patients. Continuous ambulatory peritoneal dialysis (CAPD) compensates for the low efficiency of the peritoneal membrane by its continuous nature. Nevertheless, in the last few years concern has been expressed on the adequacy of peritoneal dialysis with regard to solute removal. This was especially based on the results of the CANUSA study, showing a relationship between mortality and parameters of solute transport such as Kt/V_{urea} and creatinine clearance [1]. In the USA this has even led to very strict adequacy targets for CAPD, such as $Kt/V_{urea} \geq 2$/week and creatinine clearance ≥ 60 liters/week/1.73 m^2, as expressed in the Dialysis Outcome Quality Initiative (DOQI) [2]. Others have focused more on the importance of control of hydration state and blood pressure for the prognosis of peritoneal dialysis patients [3]. As peritoneal clearances are dependent on the diffusive capacity of the peritoneal membrane, expressed either as the dialysate/plasma ratio (D/P) [4] or mass transfer area coefficient (MTAC) [5], and the drained volume, measures to increase clearances will lead to increased removal of waste products and sometimes also to more ultrafiltration. This review focuses on the role of residual renal function, the drained volume and manipulation of the diffusive capacity of the peritoneum in augmenting the clearances of low molecular weight solutes.

RESIDUAL RENAL FUNCTION

Residual renal function may contribute importantly in the removal of solutes during peritoneal dialysis. In 118 new peritoneal dialysis patients with a mean residual GFR of 3.1 ml/min, removal by the native kidneys contributed 29% to the total Kt/V_{urea} and up to 48% of the total creatinine clearance [6]. The endogenous creatinine clearance is an inaccurate determinant of GFR in non-dialyzed patients with renal failure, because tubular secretion of creatinine may contribute considerably to the urinary excretion of this solute [7]. The mean of urea and creatinine clearance provides a reasonable estimation of inulin clearance for values below 15 ml/min in patients with chronic renal failure [8]. This approach has also been used in hemodialysis patients, where it appeared to underestimate inulin clearance by 0.5 ml/min in a GFR of 3 ml/min [9].

Key words: low molecular weight solutes, clearance, residual renal function, drained dialysate volume, diffusion in the peritoneum, GFR, transport.

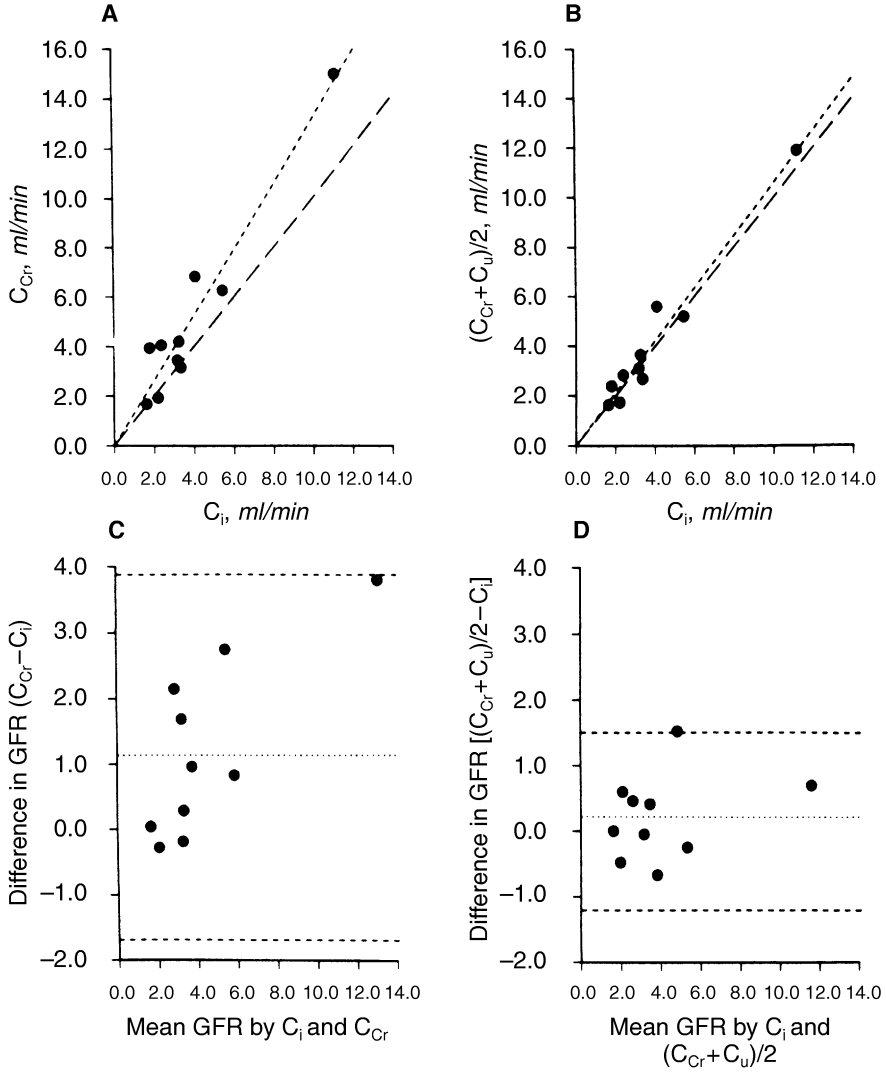

Fig. 1. Correlation between the clearance of creatinine (C_{Cr}) and inulin (C_i) (*A*; $r = 0.96$, $P < 0.01$) and between the mean of urea and creatinine clearance and inulin clearance (*B*; $r = 0.98$, $P < 0.01$), and the Bland and Altman analysis of these parameters (*C and D*). The dashed lines in the Bland and Altman analysis indicate the 95% confidence interval. Note that creatinine clearance overestimates GFR and has a larger confidence interval (C) than the mean of urea and creatinine clearance (D). (Reprinted from the *Journal of the American Society of Nephrology* [10] with permission from Williams and Wilkins Company, Baltimore, MD, USA.)

Table 1. Twenty-four hour renal and peritoneal clearances of inulin, creatinine and total paraaminohippuric acid (TPAH) in 10 stable CAPD patients

	Renal	Peritoneal
Inulin	3.2	2.6
Creatinine	4.0	4.0
TPAH	14.3	3.1
	Clearance ratios	
Creatinine/inulin	1.3	1.5
TPAH/inulin	4.5	1.2
TPAH/creatinine	3.6	0.8

Median values are given. Based on [11].

Table 2. Acute effects of furosemide, 2 × 1000 mg orally in 7 stable CAPD patients

	No furosemide	Furosemide
Urine production *ml/min*	0.27	0.66[a]
Inulin clearance *ml/min*	2.4	2.0
Creatinine clearance *ml/min*	5.4	3.7
Urea clearance *ml/min*	1.5	1.5
Fractional Na^+ excretion %	7.9	26.7[a]

Median values are given. Data are from [16]; used with permission.
[a] $P < 0.02$

For CAPD patients the mean of urea and creatinine clearance overestimated the GFR on average by 0.2 ml/min [10], as shown in Figure 1.

Residual renal function is not only comprised of GFR. Besides endocrine functions, tubular secretion is also important, especially for organic acids such as paraaminohippuric acid (Table 1). In CAPD patients who have on average an equal contribution of renal and peritoneal clearance in the removal of creatinine, the renal contribution in the removal of paraaminohippuric acid exceeded the peritoneal contribution 4 to 5 times [11]. Little is known about the toxicity of chronic exposure to these organic acids *in vivo*, but it is evident that the DOQI statement on the equivalency of residual renal and peritoneal clearances of

Table 3. Effects of drained volume and of diffusive membrane characteristics on peritoneal clearances of low- and middle-molecular weight solutes, in relation to solute size

Solute	Molecular wt *Daltons*	Effect of drained volume	Effect of diffusive membrane characteristics
Urea	60	++	−
Creatinine	113		
Urate	668		
Inulin	5,500		
β_2-microglobulin	11,800	−	++

Table 4. Effect of increasing the dialysis volume from 2 to 3 liters (1.36% glucose) on the peritoneal mass transfer of low molecular weight solutes, serum proteins and net ultrafiltration after a 4 hour dwell

Solute	2 Liters	3 Liters	% Change
Urea *mmol/4 hr*	61 ± 19	85 ± 31	39[b]
Creatinine *μmol/4 hr*	1849 ± 319	2634 ± 542	42[c]
Glucose *mmol/4 hr*	100 ± 19	138 ± 24	38[b]
β_2-microglobulin *mg/4 hr*	9.0 ± 2.2	9.5 ± 2.9	6
Albumin *mg/4 hr*	881 ± 225	938 ± 200	6
IgG *mg/4 hr*	137 ± 38	148 ± 43	8
Net ultrafiltration *ml/4 hr*	107 ± 54	−210 ± 293	−296[a]

Data are means ± SD of 8 patients. Based on [19].
[a] $P < 0.05$; [b] $P < 0.01$; [c] $P < 0.001$

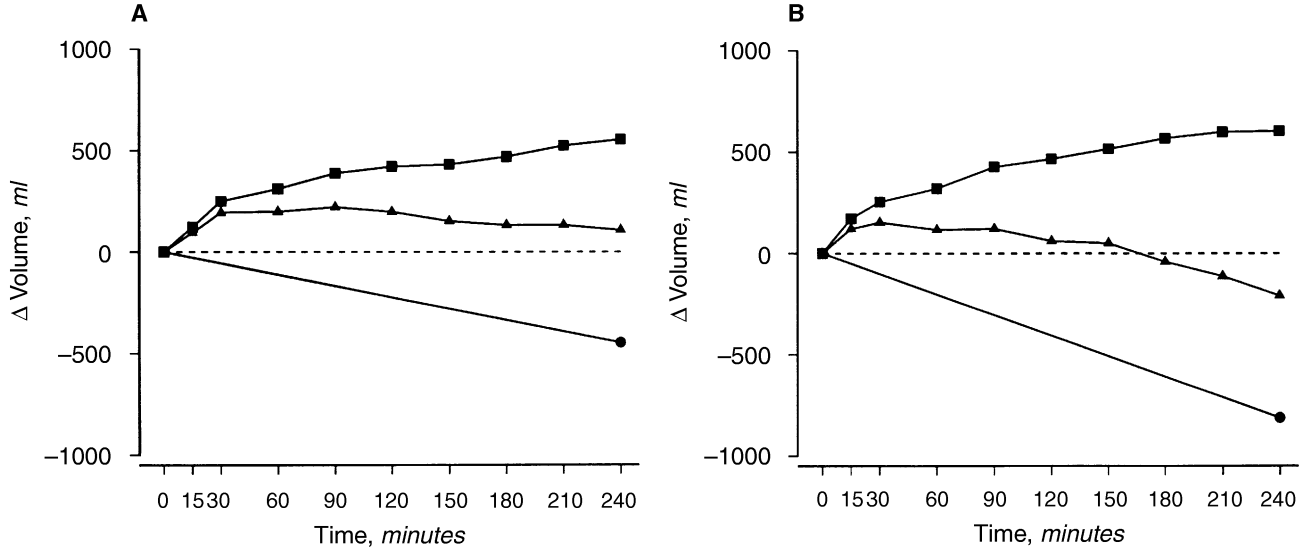

Fig. 2. Transcapillary ultrafiltration (■), effective lymphatic absorption (●) and the resulting change in intraperitoneal volume (▲) in 8 stable CAPD patients who were on a 2 liter exchange of 1.36% glucose (*A*) or with a 3 liter exchange of 1.36% glucose based dialysate (*B*). (Based on data from [19].)

small solutes is a simplification. Every ml/min loss of residual GFR is accompanied by a loss of tubular secretion of various solutes that can sometimes not be replaced by peritoneal clearance, especially when a significant amount of protein binding is present.

From the above considerations it follows that preservation or even an induced increase in residual renal function is important for overall solute removal. Many studies have shown that residual GFR is better preserved in peritoneal dialysis patients than in hemodialysis patients [12–14]. Chronic administration of high dosages of furosemide is used by some centers to increase urine volume in CAPD patients. There is some evidence that this policy may retard the progression to anuria [15]. We studied the acute effects of furosemide in seven stable CAPD patients [16]. They had a urine production ranging from 140 to 1900 ml/24 hr, median 350 ml/24 hr. Any diuretics had been discontinued two weeks before the study. The patients underwent a standard peritoneal permeability analysis (SPA) as described previously [5]. This was directly followed by a 24-hour urine collection and blood sampling for the calculation of renal clearances. Inulin (2.5 g) was administered intravenously just before the SPA. Immediately after the SPA the bladder was emptied by spontaneous voiding. This was the starting point of the 24-hour collection period. The procedure was repeated one week later, but it was preceded by the oral administration of furosemide 1000 mg twice daily, starting 24 hours before the second study period. Furosemide had no effect on peritoneal solute and fluid transport kinetics as measured with the SPA. The results with regard to renal clearances are summarized in Table 2. The urine production increased 2.5-fold, but no effect was observed on the GFR and the clearances of urea and creatinine. However, the fractional excretion of sodium increased about three times, leading to a median increase of sodium excretion of 54 mmol/24 hr. It follows from these

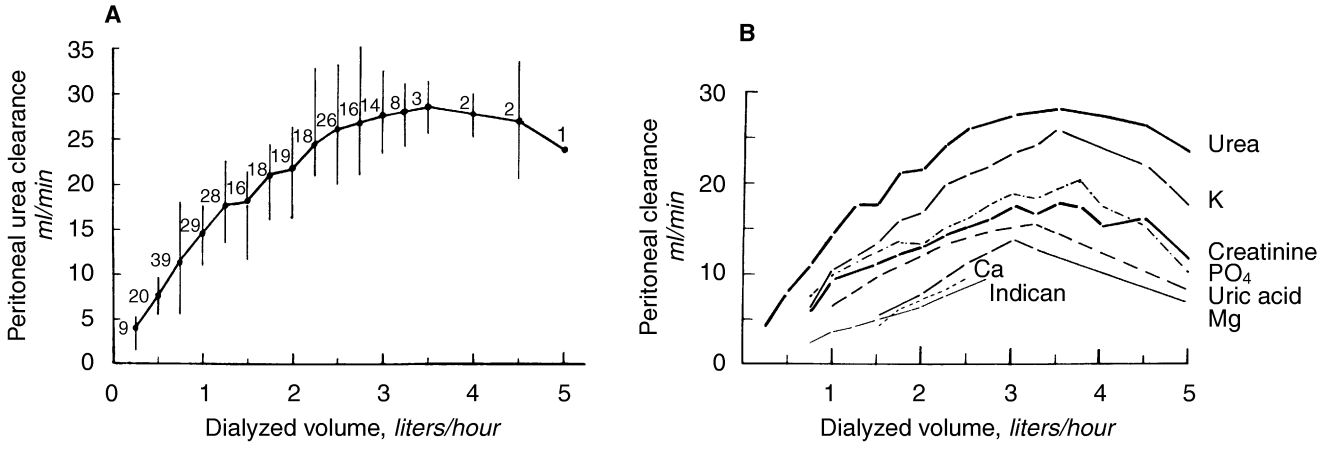

Fig. 3. Relationship between the dialyzed volume and peritoneal urea clearance (*A*) and the relationship between dialyzed volume and the clearances of various other solutes (*B*). (Reprinted from *Medicine* [23] with permission of the author and of Williams and Wilkins Company, Baltimore, MD, USA.)

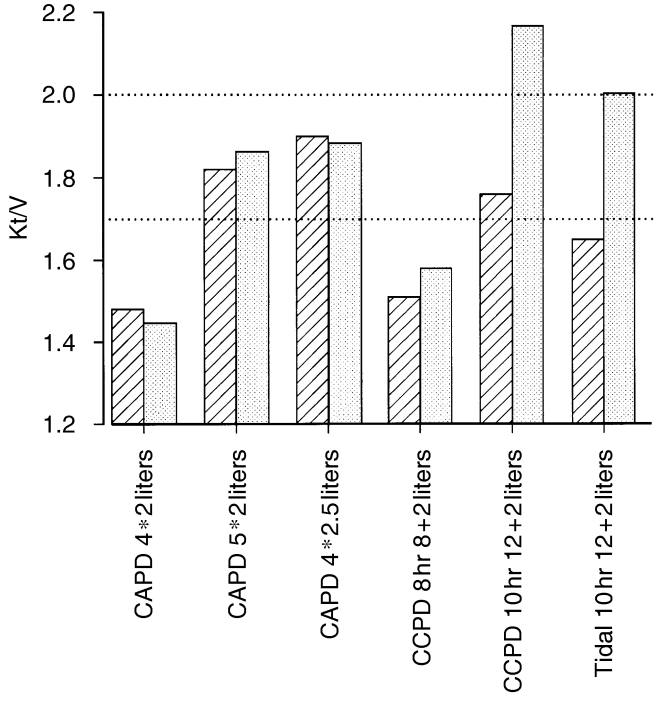

Fig. 4. Computer predictions using the PD Adequest® software program for Kt/V_{urea} using different dialysis prescriptions. Simulations were made for anuric patients with a body surface area of 1.84 m^2. The hatched bars represent the values for a D/P ratio creatinine of 0.65 in the peritoneal equilibration test with the use of only 2.27% glucose dialysate. The stippled bars represent the values for a D/P ratio creatinine of 0.89 and the use of only 3.86% glucose dialysate.

data that high dosages of furosemide increase the total removal of water and sodium from the body, but have no effect on Kt/V_{urea} and total creatinine clearance.

One study reported that an early start of hemodialysis might lead to better preservation of residual creatinine clearance [17]. No data are available on whether this might also occur in peritoneal dialysis. It is also not known whether long-term treatment with angiotensin converting enzyme (ACE) inhibitors could influence the progression to anuria in peritoneal dialysis patients.

DRAINED VOLUME

The dialysate flow rate, that is, the drained volume per unit of time, is the only determinant of the peritoneal clearance of a low molecular weight solute when a concentration equilibrium is present between plasma and dialysate. For instance, this is the case for urea during long dwells. It is different for high molecular weight solutes where no important effect of saturation of the dialysate is present, such as for serum proteins. For these macromolecules no effect of the drained volume is present [18], and the diffusive capacity of the peritoneum is the determinant of the peritoneal clearance (Table 3). The drained volume can be increased by the use of large volumes for instillation, by the application of more exchanges, and by increasing peritoneal ultrafiltration.

Increasing the dialysate volume from 2 to 3 liters of 1.36% glucose in eight stable CAPD patients had no effects on MTACs during a four hour dwell, but increased the mass transfer of low molecular weight solutes by an average of 40% (Table 4) [19]. No effect was present on the mass transfer of serum proteins. However, the effective lymphatic absorption rate measured with intraperitoneally administered autologous hemoglobin increased, with 89% probably caused by the higher intraperitoneal pressure [20, 21]. This resulted in lower net ultrafiltration after four hours with three liters of 1.36% glucose dialysate compared to two liters, as shown in Figure 2. A more recent study in rats using various volumes of 3.86% glucose dialysate confirmed the absence of an effect of fill volume on MTACs of low molecular weights solutes, as well as the augmenting effect on small solute clearances [22]. Also, the effective lymphatic absorption rate measured as the disappearance rate of ^{131}I-albumin was greater in this animal

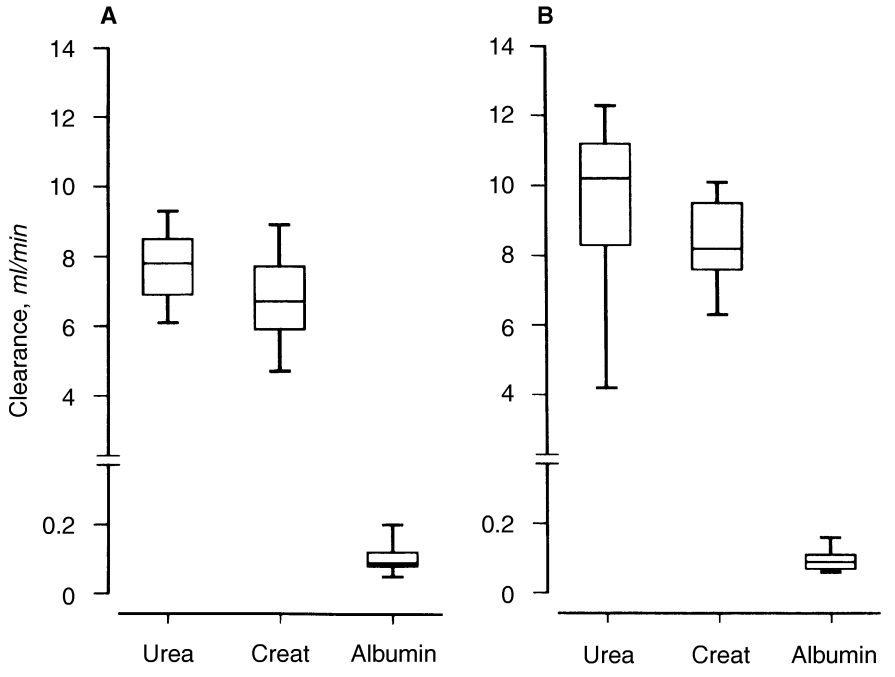

Fig. 5. Peritoneal clearances of urea, creatinine and albumin during four hours dwells with 1.36% glucose-based dialysate (*A*) and with 3.86% glucose (*B*). Results are expressed as box en whisker plots. The boxes show the median values and the 25th and 75th percentiles, and the extremes are represented by the whiskers. (Based on data from [25].)

model. Intraperitoneally administered albumin disappears from the peritoneal cavity by direct uptake into the subdiaphragmatic lymphatics and by transport across the mesothelial layer into peritoneal interstitial tissues. The latter route was especially increased after the administration of large dialysate volumes. In contrast to the study in humans, net ultrafiltration increased with higher fill volumes due to the better persistence of the osmotic gradient. The difference is explained most likely by the fact that the human studies were done with 1.36% glucose and the animal studies with 3.86% glucose. It can therefore be concluded that increasing the dialysate volume: (*1*) has no effect on the diffusive characteristics of the peritoneal membrane; (*2*) leads to greater mass transfer of low molecular weight solutes due to the higher drained volume; (*3*) leads to an increase in effective lymphatic absorption; and (*4*) has effects on transcapillary ultrafiltration that are dependent on the glucose concentration of the used dialysis fluids.

Peritoneal mass transport of low molecular weight solutes can be increased by using a larger number of dialysis exchanges. This can easily be done by using automated peritoneal dialysis (APD). However, as already shown by Boen, the maximum peritoneal urea clearance is achieved with volumes of 3 to 3.5 liters per hour (Fig. 3) [23]. This is explained by the time lost for drainage and instillation of fresh dialysis fluids. Awareness of this phenomenon has led to the concept of tidal peritoneal dialysis where only 50% of the intraperitoneal volume is exchanged. However, this will lead to a decrease in the diffusive gradient during the dwells. Whether increasing the instilled volume or increasing the number of exchanges is more efficacious is dependent on the diffusive characteristics of the peritoneal membrane. In patients with an average transport state in the PET, increasing the volume augments Kt/V more than increasing the number of exchanges. In those with high solute transport rates, Kt/V_{urea} is especially influenced by the number of exchanges. This is illustrated in Figure 4, where predictions were made using the PD Adequest® program [24]. It follows from these computer simulations that tidal peritoneal dialysis offers no real advantage with regard to small solute clearance.

The drained volume can also be augmented by increasing ultrafiltration. Net ultrafiltration in peritoneal dialysis is the difference between transcapillary ultrafiltration and effective lymphatic absorption. Transcapillary ultrafiltration can be enhanced by avoiding a very high intraperitoneal pressure and by increasing the osmotic pressure gradient, such as by using more hypertonic dwells. The use of 3.86% glucose instead of 1.36% glucose had no effect on MTACs [18, 25], but increased the clearances of urea and creatinine by an average of 25% (Fig. 5). However, evidence is accumulating that chronic exposure to these very high glucose concentrations is an important pathogenetic factor in the alterations that can develop in the peritoneal membrane after long-term peritoneal dialysis [26]. Another way to ensure high transcapillary ultrafiltration rates especially during long dwells is the use of the glucose polymer icodextrin [27].

Net ultrafiltration is also influenced by the effective lymphatic absorption rate, measured as the disappearance rate of intraperitoneally administered macromolecules. Some drugs are likely to decrease this absorption rate, leading to higher drained volumes. Examples are intraperitoneal phosphatidylcholine [28–30], oral bethanechol [31],

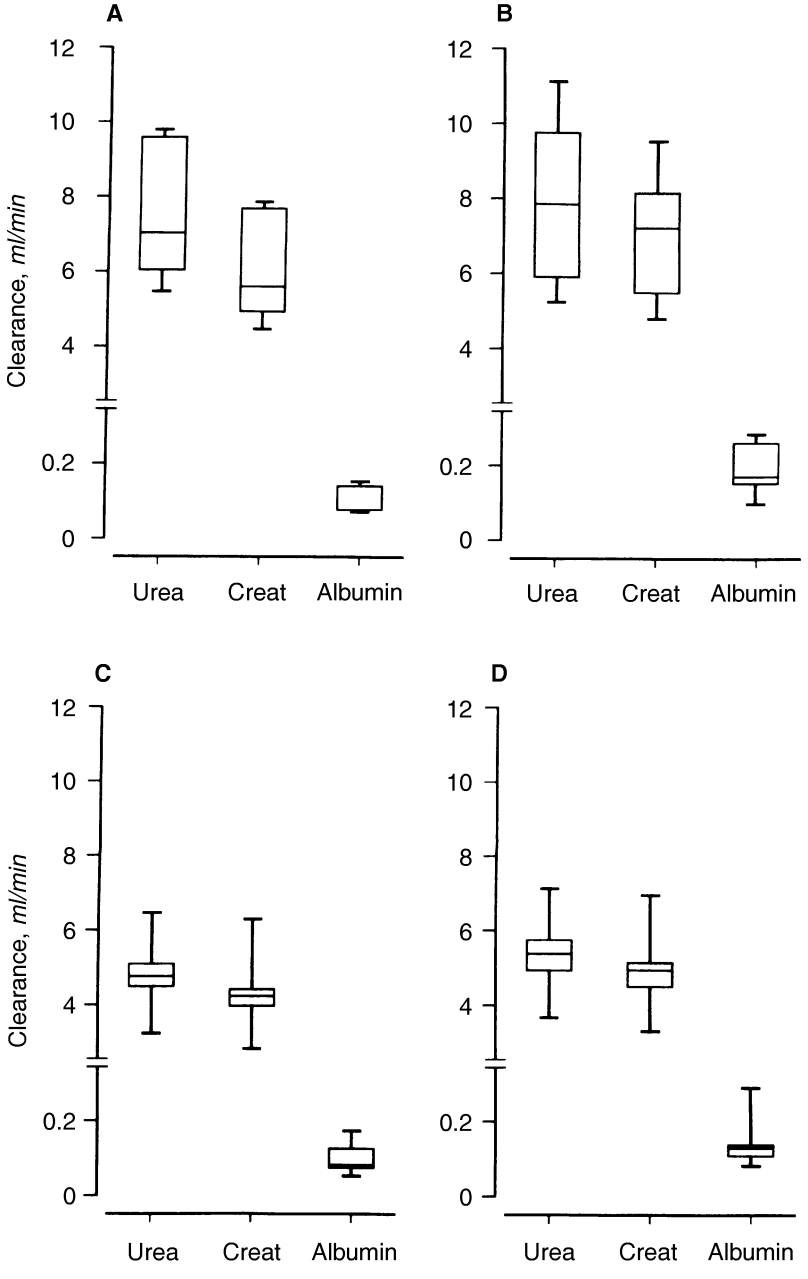

Fig. 6. Peritoneal clearances of urea, creatinine and albumin using 1.36% glucose based dialysate during a four hour dwell (*A*) and in the same patients after intraperitoneal administration of nitroprusside 4.5 mg/liter (*B*). Peritoneal clearances of the same solutes using 7.5% icodextrin based dialysate during an eight hour dwell (*C*) and in the same patient after intraperitoneal administration of nitroprusside 4.5 mg/liter (*D*). (Based on data from references [47, 48].)

and intraperitoneal hyaluronan [32]. Oral bethanechol chloride is the only one that can currently be used in CAPD patients, but its effectiveness has thus far not been confirmed in other studies.

PERITONEAL DIFFUSIVE CAPACITY

The diffusive capacity of a membrane is determined by its surface area and its permeability or size-selectivity. It has become evident that the transport of low molecular weight solutes across the peritoneal membrane is mainly dependent on its vascular surface area and hardly on its permeability [33, 34]. Consequently, MTACs or D/P ratios of low molecular weight solutes provide information on the vascular peritoneal surface area, that is, the number of perfused peritoneal capillaries or the number of pores available for transport. In the past many attempts have been made to increase the vascular surface area in animals and in IPD patients by pharmacological methods, especially by intraperitoneal administration of vasodilators. Intraperitoneal administration of the β-receptor agonist isoproterenol increased low molecular weight solute clearances in rats [35], rabbits [36] and dogs [37], but hardly increased it

in IPD patients [38]. Intraperitoneal administration of the α receptor blocker phentolamine had no effect on solute clearances in IPD patients [38]. This lack of effect was also found for the vasodilators hydralazine [38], and papaverine [39], while the effect of diazoxide was only limited [38]. Oral dipyridamole increased peritoneal inulin clearance and glucose absorption in IPD patients without a significant effect on the clearances of urea and creatinine [40]. In a subsequent study by the same authors in CAPD patients no effects were found [41]. A small number of studies has been published on effects of antihypertensives in CAPD patients. In one study oral clonidine had no effect on peritoneal creatinine clearance, but nifedipine and enalapril increased it by an average of 13% [42]. However, in another study no effect of either orally or intraperitoneally administered enalapril was found on the peritoneal clearances of urea and creatinine [43].

The effects of all these pharmacological interventions are much less than those of intraperitoneally administered nitroprusside. This direct nitric oxide donor induced marked increases in the peritoneal clearances of low molecular weights solutes in animals [35, 44], and in IPD patients [38, 45, 46]. The finding that peritoneal protein loss also increased, suggested that nitroprusside not only enlarged the vascular surface area, but also increased the permeability of the peritoneal membrane. Recently we studied the effects of intraperitoneal administration of nitroprusside 4.5 mg/liter during single dwells in stable CAPD patients [47, 48]. The drug was administered to patients with either 1.36% glucose-based dialysate and studied during four hour dwells [47], or to 7.5% icodextrin-based dialysate and studied during eight-hour dwells [48]. No effect on blood pressure was found. Both studies were done in 10 stable CAPD patients. Each patient was studied during a SPA without the administration of nitroprusside, and again on another day during a SPA with intraperitoneal nitroprusside. The interval between the two SPAs was less than one week. The effect on the clearances of urea, creatinine and albumin is shown in Figure 6. The increase in the clearance of urea during the 1.36% glucose SPA was 4% (NS), that of creatinine 16% ($P < 0.01$), and that of albumin 75% ($P < 0.01$). During the 7.5% icodextrin SPAs urea clearance increased 13%, creatinine clearance 15%, and albumin clearance 47%, $P < 0.01$ for all solutes. It could be estimated that when the glucose-based night exchange would be replaced by a 7.5% icodextrin exchange with nitroprusside, this would increase the peritoneal creatinine clearance with on average 6 liters per week and peritoneal albumin loss with 0.9 grams per day. However, these are just extrapolations based on single standardized exchanges. A clinical trial is necessary to prove whether these predictions are correct during chronic administration, and whether this can be done without damaging the peritoneal membrane.

CONCLUSIONS

Increasing the urine output in peritoneal dialysis patients with residual renal function by furosemide does not increase small solute clearances. Increasing the instilled volume of dialysis fluid and the number of exchanges both affect solute clearance, but have their limitations. Manipulation of the vascular peritoneal surface area, such as with nitroprusside, may be an interesting possibility, but more studies are needed on this subject.

Reprint requests to Raymond T. Krediet, M.D., Academic Medical Center, Renal Unit, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands.

APPENDIX

Abbreviations used in this article are: ACE, angiotensin converting enzyme; APD, automated peritoneal dialysis; DOQI, Dialysis Outcome Quality Initiative; D/P ratio, dialysis/plasma ratio; GFR, glomerular filtration rate; IPD, intermittent peritoneal dialysis; Kt/V, dialysis dose; MTAC, mass transfer area coefficient; SPA, standard peritoneal permeability analysis.

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