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Selectively increasing the clearance of protein-bound uremic solutes

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Abstract

Background. The toxicity of bound solutes could be better evaluated if we could adjust the clearance of such solutes independent of unbound solutes. This study assessed whether bound solute clearances can be increased while maintaining urea clearance constant during the extended hours of nocturnal dialysis.

Methods. Nine patients on thrice-weekly nocturnal dialysis underwent two experimental dialysis treatments 1 week apart. The experimental treatments were designed to provide the same urea clearance while providing widely different bound solute clearance. One treatment employed a large dialyzer and high dialyzate flow rate (Q_d) of 800 mL/min while blood flow (Q_b) was 270 mL/min. The other treatment employed a smaller dialyzer and Q_d of 300 mL/min while Q_b was 350 mL/min.

Results. Treatment with the large dialyzer and higher Q_d greatly increased the clearances of the bound solutes *p*-cresol sulfate (PCS: 27 ± 9 versus 14 ± 6 mL/min) and indoxyl sulfate (IS: 26 ± 8 versus 14 ± 5 mL/min) without altering the clearance of urea (204 ± 20 versus 193 ± 16 mL/min). Increasing PCS and IS clearances increased the removal of these solutes (PCS: 375 ± 200 versus 207 ± 86 mg/session; IS: 201 ± 137 versus 153 ± 74 mg/session), while urea removal was not different.

Conclusions. The removal of bound solutes can thus be increased by raising the dialyzate flow and dialyzer size above the low levels sufficient to achieve target Kt/V_{urea} during extended treatment. Selectively increasing the clearance of bound solutes provides a potential means to test their toxicity.

Keywords: bound solutes; hemodialysis; urea modeling; uremia

Introduction

Solutes that bind to plasma proteins may be important uremic toxins [1–3]. The clinical importance of such solutes could be better evaluated if we could selectively adjust their clearance by hemodialysis. The current study evaluated a means to increase the clearance of bound solutes independent of the urea clearance during nocturnal dialysis. The extended hours of nocturnal dialysis allow target Kt/V_{urea} values to be obtained with lower dialyzate flows and smaller dialyzers than are commonly used for conventional thrice-weekly treatment. Most reports of nocturnal dialysis thus describe treatment with blood flows from 200 to 300 mL/min, dialyzate flows (Qd) from 300 to 500 mL/min and small dialyzers [4–8]. Mathematical models predict that lowering the ratios of the dialyzate flow and dialyzer mass transfer area coefficient to the blood flow (Qb) will reduce the clearance of bound solutes more than the clearance of urea [9, 10]. This suggests that the removal of bound solutes is limited when low dialyzate flows and small dialyzers are employed during the extended hours of nocturnal dialysis. The current study tested the hypothesis that bound solute clearances can be increased without affecting urea clearance by increasing the dialyzate flow and mass transfer area coefficient (K_oA) relative to the blood flow during nocturnal dialysis sessions lasting 8 h.

Materials and methods

Studies were performed in nine stable hemodialysis patients receiving in-center nocturnal hemodialysis thrice weekly. Two experimental hemodialysis prescriptions were devised using a previously described mathematical model [9]. The *High* K_oA-Q_d prescription included a Rexeed 25S dialyzer (Asahi Kasei Kuraray, Tokyo, Japan), Q_d 800 mL/min and Q_b 270 mL/min, while the *Low* K_oA-Q_d prescription included an F160NR dialyzer (Fresenius Medical Care, Waltham, MA), Q_d 300 mL/min and Q_b 350 mL/min. The K_oA_{urea} values provided by the manufacturers are 1881 mL/min for the Rexeed 25S and 1064 mL/min for the F160NR and both are classified as high-flux dialyzers. Each subject was dialyzed once with each of the two experimental prescriptions in random order at midweek sessions 1 week apart. The dialysis time, ultrafiltration target, heparin therapy and dialyzate remained the same as for the patients' standard treatment. Plasma samples were obtained pre-, mid-, post- and 1 h post-dialysis. The mid- and post-dialysis plasma samples were collected from the arterial line using the low-blood-flow technique (Q_b 50 mL/min) as recommended by *Kidney Disease Outcomes Quality Initiative guidelines* [11]. Spent dialyzate from the first and second halves of each treatment was collected in separate 208-L barrels. The dialyzate volumes were determined by weight and dialyzate was mixed thoroughly prior to collection of samples for chemical analysis.

Concentrations of *p*-cresol sulfate (PCS), indoxyl sulfate (IS) and hippurate in plasma and dialyzate were measured by high-performance liquid chromatography as previously described [12]. Dialyzate PCS values were

below the limit of quantification in two patients and PCS values for these patients were not included in the analysis. Free unbound solute concentrations were measured in pre-dialysis plasma ultrafiltrates obtained using Nanosep 30K Omega separators (Pall, Ann Arbor, MI) and the unbound fraction was calculated as the ultrafiltrate concentration divided by the total concentration. Urea in plasma and dialyzate was measured using a commercial kit (1770-500; Thermo Electron Corp., Melbourne, Australia). Potassium was measured using an iSTAT-1 (Abbott, Princeton, NJ). Plasma albumin, phosphorus and amino acids were measured in the clinical laboratory.

Clearance values were calculated as the amount collected in the dialyzate divided by the log mean of the total plasma concentrations before and after the dialyzate collection. Reduction ratios were calculated as the difference between the initial and final plasma levels divided by the initial plasma level. Values are expressed as mean ± SD throughout. Statistical comparisons between the high K_oA-Q_d and low K_oA-Q_d sessions and between each bound solute and urea were performed using the Wilcoxon signed-rank sum test using SPSS software.

Results

The characteristics of the nine patients are summarized in Table 1. The patients had been maintained on in-center nocturnal hemodialysis for an average of 13 ± 8 months. Their routine prescriptions included blood flow 300 mL/min, dialyzate flow 500 mL/min and F160 or F180 dialyzers (Fresenius Medical Care). The treatment time was 480 min in eight patients and 420 min in one patient and the average monthly urea reduction ratio was 84 ± 4%.

The treatment parameters for the two experimental hemodialysis sessions (designated *High* K_oA-Q_d and *Low* K_oA-Q_d) performed 1 week apart in each patient are summarized in Table 2. The *High* K_oA-Q_d session was designed to enhance protein-bound solute clearance by employing a greater Q_d and larger dialyzer as compared to the *Low* K_oA-Q_d session. The dialyzate composition and treatment time remained the same for the two sessions and the values for pre-dialysis weight and ultrafiltration rate were similar.

The clearances, reduction ratios, pre-dialysis plasma levels and amounts removed in the dialyzate for each solute are summarized in Table 3. The urea clearances were not significantly different during the *High* K_oA-Q_d session and the *Low* K_oA-Q_d session (204 ± 20 versus 193 ± 16 mL/min). The urea reduction ratio was slightly higher during the *High* K_oA-Q_d session (86 ± 5 versus 82 ± 5%) and the amount of urea removed in the dialyzate was the same during both sessions.

As expected, clearances of the tightly bound solutes PCS and IS were much lower than the clearance of urea. And for these solutes, the *High* K_oA-Q_d prescription provided clearances that were much greater than those provided by the *Low* K_oA-Q_d prescription. For PCS, the average clearance of 27 ± 9 mL/min during the *High* K_oA-Q_d session was approximately twice the clearance of 14 ± 6 mL/min during the *Low* K_oA-Q_d session and the average ratio of the clearance values in individual subjects was 2.0 ± 0.3. The greater clearance during the *High* K_oA-Q_d session was not attributable to lesser protein binding, as the free fractions of PCS were similar for the two sessions (7.9 ± 3.9 and 7.5 ± 4.7%, respectively). The greater PCS clearance during the *High* K_oA-Q_d session resulted in a greater PCS reduction ratio. And because the pre-dialysis plasma levels were similar for the two sessions, substantially more PCS was removed with the higher clearance provided by the *High* K_oA-Q_d session than with the lower clearance provided by the *Low* K_oA-Q_d prescription (375 ± 200 versus 207 ± 86 mg).

The values for IS closely paralleled those for PCS. For IS, the average clearance was 26 ± 8 mL/min during the *High* K_oA-Q_d session as compared to 14 ± 5 mL/min during the *Low* K_oA-Q_d session and the average ratio of the clearance values in individual subjects was 1.9 ± 0.4. The greater clearance during the *High* K_oA-Q_d session was again not attributable to lesser protein binding (free fraction 7.1 ± 3.5 versus

Table 1. Patient characteristics

Dialysis vintage (years)	5 ± 4
Nocturnal dialysis vintage (months)	13 ± 8
Q_b (mL/min)	300
Q_d (mL/min)	500
Dialyzer	F160 or F180
Treatment time (min)	473 ± 20
URR (%)	84 ± 4
BMI (kg/m^2)	28 ± 9

Table 2. Hemodialysis treatment parameters

	High K_oA-Q_d	Low K_oA-Q_d
Q_b (mL/min)	270	350
Q_d (mL/min)	800	300
Dialyzer	Rexeed 25S	F160NR
Treatment time (min)	473 ± 20	473 ± 20
Pre-dialysis weight (kg)	89 ± 35	89 ± 35
Ultrafiltration rate (mL/h/kg)	2.4 ± 2.0	3.0 ± 2.6

Q_b, blood flow; Q_d, dialyzate flow.

Table 3. Solute measurements

	High K_oA-Q_d	Low K_oA-Q_d
UreaN		
Clearance (mL/min)	204 ± 20	193 ± 16
Reduction ratio (%)	86 ± 5[a]	82 ± 5
Plasma pre (mg/dL)	43 ± 7	47 ± 13
Removed in dialyzate (g)	19 ± 5	20 ± 3
PCS		
Clearance (mL/min)	27 ± 9[a,b]	14 ± 6[b]
% Free pre-dialysis	7.9 ± 3.9	7.5 ± 4.7
Reduction ratio (%)	59 ± 8[a,b]	41 ± 11[b]
Plasma pre (mg/dL)	4.7 ± 2.1	4.4 ± 2.0
Removed in dialyzate (mg)	375 ± 200[a]	207 ± 86
IS		
Clearance (mL/min)	26 ± 8[a,b]	14 ± 5[b]
% Free pre-dialysis	7.1 ± 3.5	7.0 ± 3.9
Reduction ratio (%)	66 ± 6[a,b]	46 ± 9[b]
Plasma pre (mg/dL)	2.6 ± 1.0	2.8 ± 1.3
Removed in dialyzate (mg)	201 ± 137[a]	153 ± 74
Hippurate		
Clearance (mL/min)	121 ± 14[a,b]	83 ± 13[b]
% Free pre-dialysis	52 ± 13	52 ± 12
Reduction ratio (%)	89 ± 7[a,b]	81 ± 7
Plasma pre (mg/dL)	6.8 ± 6.1	6.5 ± 4.7
Removed in dialyzate (mg)	1464 ± 1332	1236 ± 913

[a]$P < 0.05$, *High* K_oA-Q_d versus *Low* K_oA-Q_d.
[b]$P < 0.05$, clearance and reduction ratios for other solutes compared to urea.

7.0 ± 3.9%) and resulted in a greater IS reduction ratio. As was the case with PCS, average pre-dialysis plasma levels were similar for the two sessions and more IS was removed during the *High* K_oA-Q_d session than the *Low* K_oA-Q_d session (201 ± 137 versus 153 ± 74 mg). The increases in clearance achieved with the *High* K_oA-Q_d session were nearly the same for IS and PCS but the increase in amount of solute removed was less for IS, due largely to small differences in pre-dialysis concentrations of the two solutes at the two sessions.

Values for hippurate, which was ~50% protein bound, were between those for urea and the more tightly bound solutes PCS and IS. The average clearance of 121 ± 14 mL/min during the *High* K_oA-Q_d session was significantly greater than the clearance of 83 ± 13 mL/min during the *Low* K_oA-Q_d session and the average ratio of the clearance values in individual subjects was 1.5 ± 0.3. The reduction ratio was 89 ± 7% for the *High* K_oA-Q_d session and 81 ± 7% for the *Low* K_oA-Q_d session. But while the average pre-dialysis plasma levels of hippurate were similar for both sessions, the variability in levels among individual subjects was such that the increase in clearance and modest increase in reduction ratio achieved during the *High* K_oA-Q_d session were not accompanied by a significant increase in hippurate removal.

Solute concentration profiles during the experimental sessions are further depicted in Figure 1. Because the *Low* K_oA-Q_d session reduced the levels of PCS and IS by <50%, the reduction ratio for these bound solutes could be increased by the higher clearance provided by the *High* K_oA-Q_d session. There was little change in solute levels between the end of treatment and 1 h post-treatment. Statistically significant rebound was observed only for urea after the *High* K_oA-Q_d and *Low* K_oA-Q_d sessions and for hippurate after the *High* K_oA-Q_d session (2 ± 1, 3 ± 2 and 4 ± 4% of the pre-dialysis concentration, respectively). Values for clearance and concentration reduction ratio during the first and second halves of the sessions are summarized in Table 4. For the tightly bound solutes, the clearances were nearly the same during the first and second halves of each session but the concentration reduction ratios were lower during the second half of the session.

Routine plasma chemistry values pre- and post-dialysis are summarized in Table 5. Despite an average net ultrafiltration of ~2 L, plasma albumin levels did not increase significantly post-dialysis. The reduction in plasma potassium and phosphorus levels was similar for the two sessions. The reduction in total plasma amino acid levels and the amount of amino acids removed in the dialyzate were also similar for the two sessions.

Discussion

The extended treatment time used for nocturnal hemodialysis provides several potential benefits [13]. Early studies showed

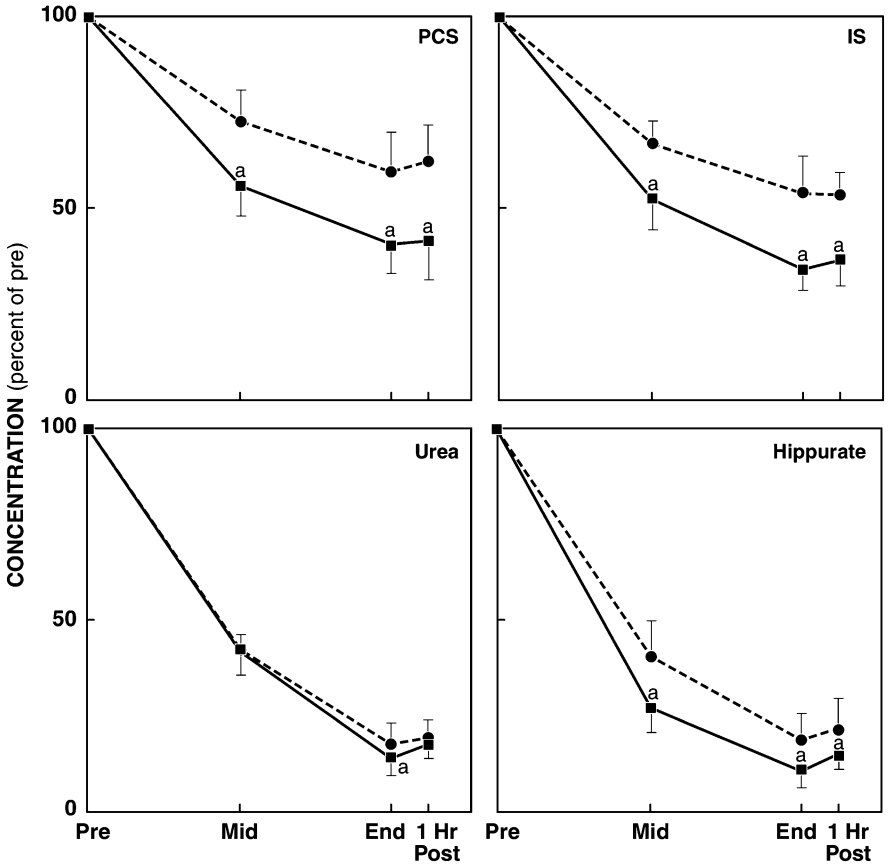

Fig. 1. Solute concentration profiles during the two experimental sessions (*High* K_oA-Q_d, solid line; *Low* K_oA-Q_d dashed line). Concentrations were measured at the beginning, middle and end of the dialysis sessions and 1 h post-dialysis. [a]$P < 0.05$, *High* K_oA-Q_d versus *Low* K_oA-Q_d.

Table 4. Comparison of the first and second halves of treatment

	High K_oA-Q_d		Low K_oA-Q_d	
	First half	Second half	First half	Second half
Urea				
Clearance (mL/min)	194 ± 21	213 ± 30	187 ± 18	200 ± 20
Reduction ratio (%)	58 ± 7	67 ± 7[a]	58 ± 4	58 ± 11
PCS				
Clearance (mL/min)	28 ± 9	26 ± 9	14 ± 6	14 ± 6
Reduction ratio (%)	44 ± 8	28 ± 6[a]	27 ± 8	19 ± 7[a]
IS				
Clearance (mL/min)	27 ± 9	24 ± 8	14 ± 5	14 ± 6
Reduction ratio (%)	48 ± 8	35 ± 7[a]	33 ± 6	19 ± 7[a]
Hippurate				
Clearance (mL/min)	116 ± 12	126 ± 22	84 ± 14	83 ± 14
Reduction ratio (%)	73 ± 15	61 ± 7[a]	59 ± 9	54 ± 14

[a]$P < 0.05$ first half versus second half.

Table 5. Other laboratory values

	High K_oA-Q_d	Low K_oA-Q_d
Albumin		
Plasma pre (g/dL)	3.7 ± 0.4	3.7 ± 0.3
Plasma post (g/dL)	3.7 ± 0.4	3.7 ± 0.4
Percent increase (%)	0 ± 8	1 ± 8
Potassium		
Plasma pre (mmol/L)	4.4 ± 0.5	4.5 ± 0.4
Plasma post (mmol/L)	3.2 ± 0.5	3.1 ± 0.4
Reduction ratio (%)	26 ± 13	29 ± 8
Phosphorus		
Plasma pre (mg/dL)	5.7 ± 1.3	6.2 ± 1.3
Plasma post (mg/dL)	1.9 ± 0.6	2.3 ± 0.6
Reduction ratio (%)	66 ± 7	62 ± 5
Total amino acids		
Plasma pre (mg/dL)	30 ± 9	33 ± 7
Plasma post (mg/dL)	18 ± 6	23 ± 9
Reduction ratio (%)	38 ± 17	29 ± 17
Removed in dialyzate (g)	13 ± 4	14 ± 4

that home treatments performed five to six nights per week for a total of 30–48 h improved blood pressure control and reduced left ventricular mass [14–16]. These beneficial effects were attributed to improved fluid management. In addition, home nocturnal treatment improved phosphorus control and reduced levels of the low-molecular-weight protein β_2-microglobulin [14, 16, 17]. The recently published randomized control trial of frequent nocturnal hemodialysis confirmed these improvements in blood pressure and phosphorus control [18]. More recent studies have shown that in-center nocturnal treatment performed thrice weekly provides similar benefits [4–7, 19].

Because standard Kt/V_{urea} target values are easily achieved during extended treatment, most nocturnal hemodialysis programs have prescribed lower values for Q_b, Q_d and K_oA than those used for conventional in-center treatment [5–8]. Thus, Lacson *et al.* [7] reported that treatments with an average Q_b of 306 ± 58 mL/min, Q_d of 496 ± 118 mL/min and dialyzer surface area of 1.6 ± 0.1 m^2 provided an average eKt/V_{urea} of 2.2 ± 0.6 in patients receiving in-center nocturnal dialysis from a large provider. Most other reports of in-center nocturnal dialysis also describe dialyzate flows and dialyzer sizes ranging from 300 to 500 mL/min and 1.2 to 1.5 m^2 though dialyzate flows of 600–750 mL/min and larger dialyzers have been used in some centers [4].

As long as Kt/V_{urea} is used as a measure of adequacy, it is reasonable to employ submaximal flows and small dialyzers for extended treatments. Little if any benefit was obtained by increasing eKt/V_{urea} from 1.2 to 1.5 in the HEMO study, and common nocturnal prescriptions provide eKt/V values well >1.5 even though they employ low dialyzate flows and small dialyzers [20]. Moreover, urea reduction ratios during most nocturnal treatments are so high that increasing urea clearance and Kt/V_{urea} would not cause a notable reduction in the plasma urea levels.

There are numerous solutes, however, that accumulate in kidney failure but do not behave like urea [21–23]. One potentially important group of such solutes includes small solutes that bind to plasma proteins [1, 24]. The dialytic clearance of these solutes is restricted because only the free portion is available for diffusion across the dialysis membrane. Dialysis modeling predicts that the clearance of bound solutes can be increased by increasing K_oA and Q_d relative to Q_b. Increasing the Q_d maintains the transmembrane concentration gradient by keeping the dialyzate solute concentration below the free solute concentration in the plasma [10]. Increasing K_oA increases transmembrane solute diffusion while the free solute concentration in the plasma limits the transmembrane concentration gradient. These measures can increase clearance for bound solutes like IS and PCS because as free solute diffuses across the membrane, solute is released from albumin to maintain equilibrium between the free and bound portions as governed by the association constant. This tends to maintain the free solute level and allows the solute clearance to rise to values which are much higher than the product of the plasma flow and the free solute concentration at the dialyzer blood inlet. It should be noted that increasing Q_d would not be expected to increase the clearance of solutes of large size, for which clearance by conventional dialysis is determined almost exclusively by K_oA [25].

During short dialysis sessions, a high Q_b is required to achieve target urea clearances and Kt/V_{urea} values for patients of average size. When Q_b is high, the increases in K_oA and Q_d required to greatly increase bound solute clearances can be obtained only by using two machines to increase Q_d above the standard single machine capacity of 800 mL/min and by using two dialyzers to increase K_oA [12]. The current study showed that extended treatment provides an opportunity to increase bound solute clearances independent of urea clearance using standard equipment. We used the model described by Walther *et al.* [9] to develop dialysis prescriptions that would provide the same urea clearance but greatly different bound solute clearances. The *High* K_oA-Q_d prescription employed the maximum K_oA and Q_d values available to us. To keep urea clearance nearly the same, Q_b was increased slightly above the level of the patients' regular prescription for the *Low* K_oA-Q_d prescription and reduced slightly below this level for the *High* K_oA-Q_d prescription.

The effect of the experimental prescriptions on solute clearances conformed to the predictions of the model. Compared to the *Low* K_oA-Q_d prescription, the *High* K_oA-Q_d prescription increased clearances of the tightly bound solutes PCS and IS by 105 ± 34 and 88 ± 35%, respectively. The clearance of the less tightly bound solute hippurate increased by 48 ± 31% and the clearance of urea did not increase significantly. Both prescriptions provided more than adequate dialysis by conventional standards.

Increasing solute clearances can provide benefit only if it increases solute removal. For urea, the clearances provided by both our experimental prescriptions and the patients' usual nocturnal prescriptions achieved a >80% reduction ratio. We could have increased urea clearance by increasing Q_b along with K_oA and Q_d but this would not have notably increased the removal of urea. The hippurate clearance provided by our *Low* K_oA-Q_d prescription also achieved a >80% reduction ratio. Even a larger increase in clearance than that provided by our *High* K_oA-Q_d prescription could thus not have greatly increased the removal of hippurate. The results for PCS and IS, however, were very different. With the *Low* K_oA-Q_d prescription, the reduction ratios for these solutes averaged <50% and the increases in clearance provided by the *High* K_oA-Q_d prescription therefore increased solute removal significantly. Of note, the dependence of bound solute clearance on dialyzate flow could account for the recent finding that in contrast to the removal of urea, phosphorus and β_2-microglobulin, the removal of bound solutes was not increased when dialyzate flow was reduced while dialysis duration was extended [26, 27].

The amount of a solute removed by dialysis also depends on the solute's distribution among various body compartments. If PCS and IS are modeled as being removed from a single compartment of constant volume, we would obtain average volumes of distribution for these solutes of 0.13–0.15 L/kg body weight. Meijers *et al.* [28] found, however, that though clearances of PCS and IS remained constant during extended dialysis sessions, the plasma concentrations of these solutes were reduced by lesser fractions during the second half than the first half of the sessions. The current study confirmed this previous finding, which is inconsistent with solute removal from a single compartment. Further experiments will be required to elucidate the compartmental behavior of PCS and IS.

Increasing clearances could potentially increase the removal of valuable solutes as well as uremic wastes. We restricted the clearance of small unbound solutes by adjusting Q_b downward when K_oA and Q_d were increased. This prevented increased loss of amino acids and presumably of other valuable unbound solutes during the *High* K_oA-Q_d session. The *High* K_oA-Q_d session could also increase the loss of valuable bound solutes. Valuable bound solutes such as vitamin B_{12}, thyroxine and testosterone are, however, very tightly bound to specific carrier proteins. Significant amounts of these solutes would be removed only if K_oA and Q_d were increased to much higher values than we achieved.

There is considerable, albeit inconclusive, evidence that protein-bound uremic solutes are toxic [1]. Particularly, strong evidence has been assembled for the toxicity of IS and PCS [2, 3, 29–32]. The current study shows that during extended treatment, the clearances of these solutes can be increased without altering urea clearance and using standard equipment. A particularly large increase in bound solute clearances can be obtained during nocturnal dialysis because target Kt/V_{urea} values are achieved with relatively low K_oA and Q_d values. But bound solute clearances could also be increased in other settings in which submaximal values of K_oA and Q_d are now employed. Submaximal dialyzate flows are regularly prescribed because increasing Q_d to >1.2–1.5 times Q_b increases the cost of treatment without improving its effectiveness as judged by Kt/V_{urea} [33, 34]. Many centers outside the USA employ treatments lasting 4 h or longer and obtain target Kt/V_{urea} values with Q_d values ~500 mL/min. We would predict that increasing Q_d from 500 mL/min to 800 mL/min would increase the clearances of PCS and IS by ~20% with commonly used dialyzers, while increasing the urea clearance by only ~5%.

Bound solute clearances can also be increased by combining convective with diffusive clearance in hemodiafiltration treatments [35, 36]. High convective flows are required, however, and clearances of unbound solutes are increased along with clearances of bound solutes. The present results offer a means to increase the clearance of bound solutes while holding constant the clearance of urea and other small unbound compounds. This approach could provide a means for further testing the contribution of protein-bound solutes to morbidity in end-stage renal disease.

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(See related article by Basile and Lomonte. *Kt/V* urea does not tell it all. *Nephrol Dial Transplant* 2012; 27: 1284–1287.)

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