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The post-hemodialysis rebound: Predicting and quantifying its effect on Kt/V

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The post-hemodialysis rebound: Predicting and quantifying its effect on Kt/V. Immediately after hemodialysis, the urea concentration rebounds upwards as urea continues to be transferred into the arterial circulation from peripheral body compartments. This rebound takes at least 30 minutes to complete. Hemodialysis is quantified as the Kt/V, calculated prom pre- and post-dialysis urea samples. Unless the post-dialysis sample is taken at least 30 minutes after dialysis, the Kt/V will be overestimated. This overestimation will be relatively greater in short high-efficiency dialyses, which have greater post-dialysis rebounds. We propose a method of correction that uses only the conventional pre- and immediate post-dialysis samples and is based on the physiologically-appropriate patient clearance time (tp). This is the time needed to clear all body compartments when the dialyzer clearance is infinite. The tp can be calculated from the pre-, immediate post- and 30-minute post-dialysis urea concentrations and was 35 minutes (SD 16) in 29 patients undergoing short (149 min) hemodiafiltration and standard (243 min) hemodialysis the following week. There was no significant difference between tp values calculated during the two treatments. Standard Kt/V can be corrected by multiplying by t/(t + tp) and dialysis time should be increased by tp × Kt/V minutes to compensate for the rebound. Despite individual variations in tp, a value of tp = 35 was sufficient to correct Kt/V in all patients. Kt/V corrected in this way agreed with Kt/V calculated using a 60-minute post-dialysis sample ($r = 0.856$, $P < 0.001$). The method predicted the 60-minute post-rebound concentration (SE 0.5 mM, $r = 0.983$, $P < 0.001$) and the addition of 35 minutes to the treatment time corrected for the rebound in both conventional and short treatments. Similar simple equations corrected the error in V caused by rebound effects.

The Kt/V is now the preferred method of quantifying dialysis [1], where K is the dialyzer clearance rate, V is the urea distribution volume (the body water volume) and t is the duration of the dialysis session. Kt/V is in effect the cleared volume/patient volume ratio. Kt/V can be controlled by varying dialysis time and clearance rate. Nutritional status, uremic symptoms and clinical outcome have been shown to relate to the Kt/V delivered to the patient. The Kt/V concept allows prospective predictions and planning of the dialysis. An estimate of probable Kt/V may be obtained by using a value of V calculated from the Watson equation [2] (or from body wt × 0.57), K read from the dialyzer data-sheet, and t, the proposed dialysis time. The dialysis time needed to achieve a desired Kt/V (dKt/V) may be calculated from the equation

$$t = dKt/V \times \frac{V}{K}$$

Single-pool Kt/V (Kt/V_{sp})

Since V and K cannot easily be measured accurately, Kt/V is normally measured directly from pre- and immediate post-dialysis blood urea concentrations using the equation:

$$Kt/V = \ln\left(\frac{pre}{post}\right)$$

Kt/V can be calculated precisely in this way since values for K and V are not required. Calibration errors in urea measurement are also irrelevant as only the ratio of pre/post-concentrations affect the result. More complex versions of this equation correct for the effects of residual renal function, urea generation and ultrafiltration during dialysis. These require an approximate value for K (usually calculated from the dialyzer data, blood and dialysate flow rates). Since the relative contribution of these factors to Kt/V is small, errors in K do not have a great influence on calculated Kt/V.

Post-dialysis rebound

The rate at which urea is removed from the patient depends not only on the dialyzer clearance, K, but also on the rate at which urea is transferred from peripheral compartments of the patient's body into the fistula [3]. While it is possible to increase K (using higher blood flow rate or larger dialyzer), the rate of internal transfer of urea is a property of the patient and cannot be manipulated so easily. The effect of this internal transfer is to reduce the effective clearance and to cause a rapid upward rebound of blood urea concentration as urea continues to be transferred into the central circulation after the end of dialysis. These effects are relatively greater in short, rapid dialyses.

The major component of the post-dialysis rebound is due to solute transfer between compartments [4], such as cells, gut, regions of the body where there is relatively low blood flow, the main blood circulation and the fistula. The mechanism of solute transfer between compartments may be diffusion, for example

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cross cell membranes, or it may be flow, for example from poorly perfused areas into the main circulation.

A smaller component of the post-dialysis rebound is caused by cardiopulmonary recirculation. Solute concentrations measured in the fistula normally represent only those in the arterial tree and are significantly lower than the those in the vena cava. This is because some dialyzed blood entering the fistula recirculates to the fistula through heart and lungs by-passing the systemic circulation. Concentrations in the fistula rebound upwards after dialysis as the recirculated blood clears the pulmonary circulation. This component of the post-dialysis rebound takes about one minute [5].

Equilibrated Kt/V (Kt/V_{eq})

Ideally, an equilibrated Kt/V (Kt/V_{eq}) should be calculated using a post-dialysis sample taken after the rebound is complete (at least 30 min post-dialysis). This Kt/V_{eq} will reflect the relative mass of urea removed from the patient, allowing for the effects of recirculation and inter-compartment transfer. The conventional Kt/V_{sp} using an immediate post-dialysis sample overestimates Kt/V_{eq} by up to 25% and is an inadequate measure of dialysis, especially high-efficiency treatments [6, 7]. To achieve a target Kt/V_{eq}, it is necessary to prescribe a higher Kt/V_{sp} [8], again especially in high-efficiency treatments.

V_{sp} and V_{eq}

Although precise values for K and t are not needed to calculate Kt/V, errors in these inputs will result in an inversely proportional error in V. The values Vsp and V_{eq} are virtual volumes and are only equivalent to the "real" urea distribution volume (V) if precise values for K and t are known and if single-pool kinetics apply. Since rebound effects always cause Kt/V_{eq} to be lower than Kt/V_{sp}, it follows that V_{eq} is always higher than V_{sp}. The value V_{eq} is greater than the "real" urea distribution volume, although the term Kt/V_{eq} will correctly reflect the dose of dialysis delivered. The value V_{sp} is less than V if $Kt/V_{eq} < 1$ and greater than V if $Kt/V_{eq} > 1$ [7]. Historically, dialyses have generally delivered Kt/V_{eq} around 1, at which point V_{sp} and V are similar and have been used interchangeably. The differences between the virtual volumes V_{sp} and V_{eq} and the "real" V increase with increasing efficiency of dialysis.

As part of the quality assurance of the dialysis process, V_{sp} is commonly calculated from the measured Kt/V_{sp}, t and an assumed value for K. If rebound effects are ignored and the expected K has been delivered throughout the treatment, V_{sp} should be close to the V calculated independently (such as the Watson equation [2]). If Kt is underdelivered for any reason, V_{sp} should be higher than expected, alerting the physician. If this approach is taken, V_{sp} should be corrected for rebound effects using an appropriate algorithm [7].

The Smye method

Smye et al [9] observed that the mathematics of the two-pool urea kinetic model predict that, after approximately 80 minutes of dialysis, the log urea concentrations in both the arterial blood and the total body water (equilibrated) fall linearly at an almost identical slope (Fig. 1). The difference between the two intercepts is equal to the upward rebound after dialysis. Based on this, Smye proposed an equation to predict the equilibrated (post-rebound) urea concentration (C_{eq}) using pre- and post-dialysis arterial

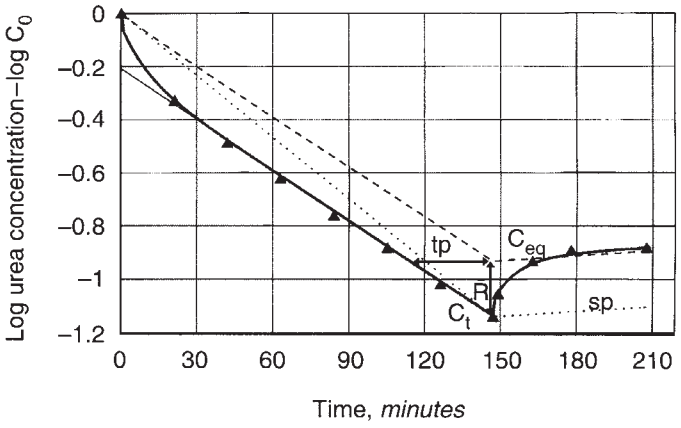

Fig. 1. *The fall in log urea concentration during short hemodiafiltration.* The lines represent concentrations in arterial blood calculated by a double-pool (thin solid line) and single-pool (dotted) models fitted to the patients data. The slope of the single-pool log concentration (C_{sp}) is equal to K/V_{sp}. The dashed line represents the equilibrated concentration. After the first 40 minutes of dialysis, both arterial and equilibrated log concentrations fall linearly at the same slope equal to K/V_{eq}. The value tp is the time dimension separating the two regressions (horizontal double-headed arrow). The rebound (R, vertical double headed arrow) is equal to $Kt/V_{sp} - Kt/V_{eq}$ and $\log(C_t) - \log(C_{eq})$.

samples (C_0, C_t) and an additional sample (C_{int}) taken at a known time after the start of dialysis (t_{int}), at about 90 minutes (equation 1 in the **Appendix**).

The Daugirdas method

Daugirdas and Schneditz [10] observed that the difference between the single-pool Kt/V (Kt/V_{sp}) and Kt/V_{eq} is proportional to K/V and that Kt/Veq could be predicted with clinically useful precision from Kt/V_{sp} and K/V (equation 2). This relationship is predicted by the regional blood flow model and the 2-pool diffusion model provided that the blood flows and inter-compartment diffusion coefficients are proportional to V.

Patient clearance time

We observed that the time separating Smye's two log-linear parallel slopes is constant whatever the rate of dialysis. This is consistent with Daugirdas's findings. This time represents both inter-compartment transfer and cardio-pulmonary recirculation. We have called this the patient clearance time (tp) [11]. It can be considered as the time needed to clear all parts of the body (so that $Kt/V_{eq} = 1$) when dialyzer clearance is infinite. If a two-pool model is assumed, the value of tp is equal to $Vi/Ki \times Vi/V$ where Vi is the volume of the peripheral compartment and Ki is the inter-compartment mass transfer rate (flow rate or diffusion coefficient). The component due to cardio-pulmonary recirculation can similarly be calculated from V/cardiac output. Using Ki, Vi and Vi/V values suggested in the literature, tp should have a value around 30 minutes. The mathematics of these derivations become more complex when more realistic multi-compartment models are used. The value of tp is specific for individual patients and solutes and independent of the rate and duration of dialysis. The value tp is sufficient to quantify inter-compartment disequilibrium and rebound effects whatever their mechanism.

By a re-arrangement of Smye's equation and according to the

log-linear approximation model, tp may be calculated from equation 3, where C_{eq} is the measured post-rebound concentration with an allowance for solute generation. Further re-arrangements yield equations 4 to 8 which can be used to correct for multi-compartment effects. Equation 4 predicts the post-rebound concentration from pre- and immediate post-dialysis concentrations. This predicted concentration may be used to calculate Kt/V_{eq} and NPCR without the need for a third sample. Equations 5 and 6 correct Kt/V_{sp} and V_{sp} calculated conventionally, using pre- and immediate post-dialysis concentrations in the single-pool equations. Equation 7 corrects the error in V_{sp} which results from using the post rebound concentration in the single-pool equation. In the prescription of dialysis, a corrected time taking rebound into account may be calculated using equation 8.

If, as shown by Daugirdas, the rate of inter-compartment transfer is a relatively constant function of V, then the value of tp will not significantly differ between patients. In this case, tp need not be measured but a mean value used in the equations.

Since the tp concept is based on Smye's analysis, it also is subject to the limitations of that approach. Smye's approximation produces results which are almost identical to precise multi-compartment analysis if dialysis times are significantly greater than the tp value (such as $2 \times tp$). The tp method breaks down when $t < tp$.

The purpose of this paper is to compare methods of rebound correction and to test the patient clearance time method.

Method

Patients

Twenty-nine stable chronic hemodialysis patients gave informed consent to be studied. Their median age was 54 years (range 19 to 81). All patients were shown to have no access recirculation by a saline-dilution method [12] with a sensitivity of 5%.

Hemodialysis

All dialyses were performed using Fresenius 2008D hemodialysis machines, bicarbonate dialysis fluid, polysulfone dialyzers (Fresenius F60 and HF80). Blood flow rates were 253 to 545 ml/min and dialysate flow rates were 500 to 800 ml/min.

Hemodiafiltration

Hemodiafiltration (HDF) was performed using the same equipment as for HD but 100 to 120 ml/min filtration was performed simultaneously. Replacement fluid was generated by filtration of the dialysate using the Fresenius on-line HDF system.

Protocol

Patients were studied during a short HDF (median 148 min) and a conventional HD (median 248 min) on consecutive weeks and the same day of the week. The prescribed times (t) were calculated for both conventional HD and short HDF using equation 8 with desired $Kt/V = 1$, $tp = 30$, V calculated using a 2-pool model in previous dialyses and K from previous *in vivo* measurements under the same conditions.

Samples were taken from the arterial needle before the start of HD/HDF (C_0) and from the arterial line at six equally spaced time intervals during the HD/HDF and at the end of the treatment (C_t) without slowing the blood pump. Further samples were taken at 2, 15, 30 and 60 minutes post-dialysis from the fistula needle. The washback was performed after the two minutes sample. Clearance was calculated from simultaneous samples taken from arterial and venous lines approximately 20 minutes after the start of HD/HDF.

Sample assay

Concentrations of urea and creatinine in lithium-heparin anticoagulated plasma were measured using a Hitachi-717 autoanalyzer. The coefficient of variation (CV) for the method was 1.76% and 1.14%, respectively. Hematocrit was measured in the pre-dialysis sample by the microcentrifuge method.

Clearance rates

The ultrafiltration and interdialytic fluid gain rates (Qf and QW) were calculated from pre- and post-dialysis weight. The blood flow rate (Qb) was measured after the dialysis by timed volumetric measurement under the same conditions as obtained during dialysis. Dialyzer clearance was calculated from dialyzer inlet and outlet concentration measurements, taking Qb, Qf and hematocrit into account. Residual renal urea clearance (Kr) was calculated from the volume and urea concentration in an interdialytic timed urine collection and the urea concentration in timed blood samples at the beginning and end of the interdialytic period.

Equilibrated post-dialysis urea concentration (C_{eq})

The measured 60-minute post-dialysis urea concentration was adjusted to take account of urea generation by subtracting $G/V \times 60$. C_{eq} was also predicted by the Smye equation (equation 1) and the tp method (equation 4 using $tp = 35$ for urea and $tp = 66$ for creatinine).

Single-pool Kt/V, V and NPCR

Kt/V_{sp}, V_{sp} and $NPCR_{sp}$ were calculated from the measured K, Kr, Qf, QW, dialysis time (t), pre- and immediate post-dialysis urea concentrations (C_0 and C_t) using the single-pool method. Kt/V_{eq}, V_{eq} and $NPCR_{eq}$ were calculated in the same way but using C_{eq} instead of C_t in the equations. $V_{i1} - V_{i6}$ were calculated using the six intradialytic samples instead of C_t in the single-pool equation.

Calculation of tp

Values for tp were calculated from t, C_0, C_t and C_{eq} using equation 3. Values were calculated independently for each patient during conventional HD and short HDF. Mean values of $tp = 35$ for urea, $tp = 66$ for creatinine were used in equations 5 to 7 to correct V_{sp}, V_{eq} and Kt/V_{sp}.

Data analysis

Paired data were analyzed by parametric and non-parametric analysis as appropriate. Agreement between measured and calculated concentrations was quantified by linear regression, standard error (SE; the average absolute difference between pairs) and Bland-Altman analysis [13].

Results

The median residual renal urea clearance was 1.95 ml/min (range 0 to 4.53). The mean measured values for urea and creatinine K were 285 (± SD 24) and 234 ± 21 ml/min for the short HDF and 164 ± 23 and 113 ± 19 ml/min for the conventional HD.

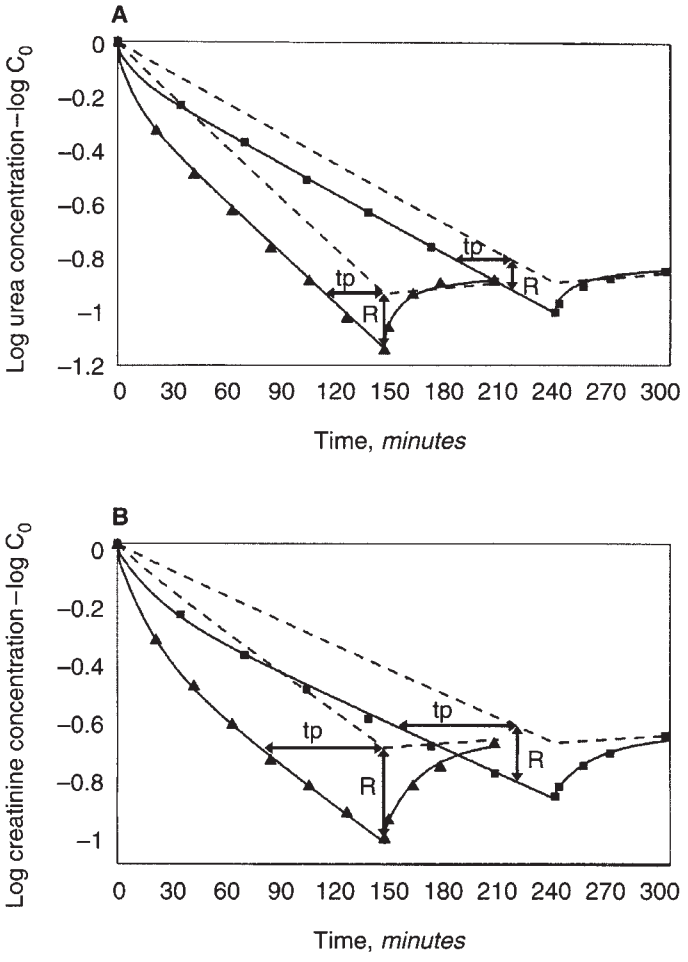

Fig. 2. *The symbols represent the mean of 29 urea concentration (A) and creatinine concentration measurements (B) made in different patients undergoing short HDF (triangles) and conventional HD (squares) on consecutive weeks.* The lines are as in Figure 1. Although K/V_{eq} is greater in short HDF compared to conventional HD, tp is the same. R is equal to $K/V_{eq} \times$ tp. In both treatments, 30 minutes were added to the dialysis time calculated by single-pool model. Although C_t is lower and Kt/V_{sp} higher in the short treatment, C_{eq} and Kt/V_{eq} are similar, indicating that the addition of 30 minutes has effectively compensated for the rebound in both conventional and short treatments.

Table 1. Comparison between conventional HD and short HDF in the same patients

		Conventional HD		Short HDF			
		Mean	SD	mean	SD	SE	*P*
Urea							
C_0	*mM*	24.8	6.0	24.4	5.8	3.2	NS
C_{eq}	*mM*	10.4	3.1	9.9	2.9	1.6	NS
C_t	*mM*	9.2	2.6	7.8	2.3	2.0	< 0.005
Kt/V_{eq}		1.091	0.119	1.047	0.141	0.086	NS
Kt/V_{sp}		1.233	0.130	1.301	0.149	0.137	< 0.005
tp	*min*	33	15	37	16	11	NS
Creatinine							
C_0	*μM*	943	185	934	195	47	NS
C_{Eq}	*μM*	478	90	463	106	32	< 0.05
C_t	*μM*	395	78	340	78	58	< 0.001
Kt/V_{eq}		0.835	0.055	0.804	0.082	0.055	< 0.05
Kt/V_{sp}		1.056	0.098	1.147	0.092	0.110	< 0.005
tp	*min*	67	15	65	11	10	NS
t	*min*	243	14	149	17		

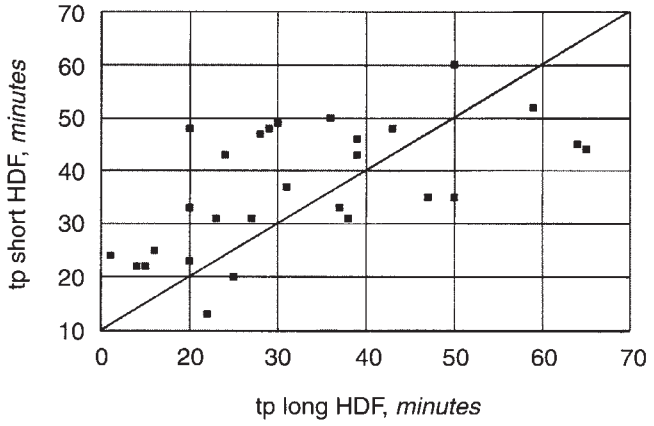

Fig. 3. *The value of urea tp calculated from C_0, C_t and C_{eq} after both conventional HD and short HDF treatments.* Regression plot with line of identity. No common data were used to calculate any two tp values. The patient's tp values tend to be reproducible despite different dialysis conditions.

Post-dialysis rebound

The urea and creatinine rebound ($\log C_{eq} - \log C_t$) was relatively greater after the short HDF than the conventional HD (Fig. 2 and Table 1). The concentrations 60 minutes after the short HDF were similar to those after the conventional HD (Table 1).

Effect of rebound on Kt/V

Urea and creatinine Kt/Vs calculated from pre- and immediate post-dialysis concentrations using the single-pool model (Kt/V_{sp}) were 19% and 35% higher than those calculated using the 60-minute post-dialysis concentration (Kt/V_{eq}) (Table 1). This overestimation of Kt/V was significantly greater during the short HDF than the conventional dialysis (23% vs. 14%, $P < 0.001$, $N = 29$). The overestimation of urea Kt/V by the single pool model was linearly proportional to K/V ($Kt/V_{sp} - Kt/V_{eq} = K/V \times 35$, $r = 0.510$, $P < 0.005$).

Individual tp values

The tp measured during the HDF was 33 (± SD 15) minutes for urea and 67 ± 15 minutes for creatinine (Table 1). These tp values were similar when calculated during the conventional dialysis (37 ± 16 for urea, 65 ± 11 for creatinine). The standard error between the tp measured during short HDF and conventional HD was 11 minutes for urea and 10 for creatinine. There was a significant correlation between tp values calculated during the short HDF and conventional HD (urea $r = 0.656$, creatinine $r = 0.679$, $P < 0.001$; Fig. 3).

The urea Kt/V_{eq} for the short HDF correlated negatively with tp measured during the conventional HD ($r = -0.526$, $P < 0.05$; Fig. 4). Arterial creatinine concentration measured before the conventional HD correlated significantly with tp measured during the short HDF ($r = 0.489$, $P < 0.01$). Similarly, arterial urea concentrations measured before the short HDF correlated with tp measured during the conventional HD ($r = 0.460$, $P < 0.01$; Fig. 4).

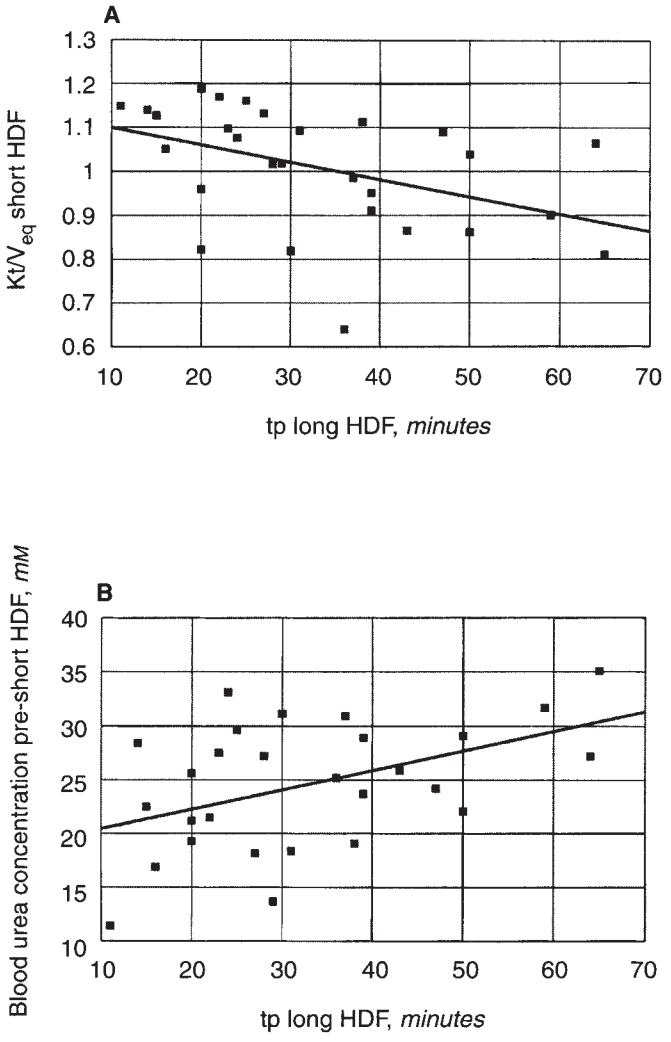

Fig. 4. *Relationship between tp calculated during the conventional HD and adequacy parameters calculated during short HDF in the same patient the following week.* Regression lines are shown. Patients with the greatest tp tend to have the lowest Kt/V_{eq} (**A**) and the highest pre-dialysis blood urea concentration (**B**).

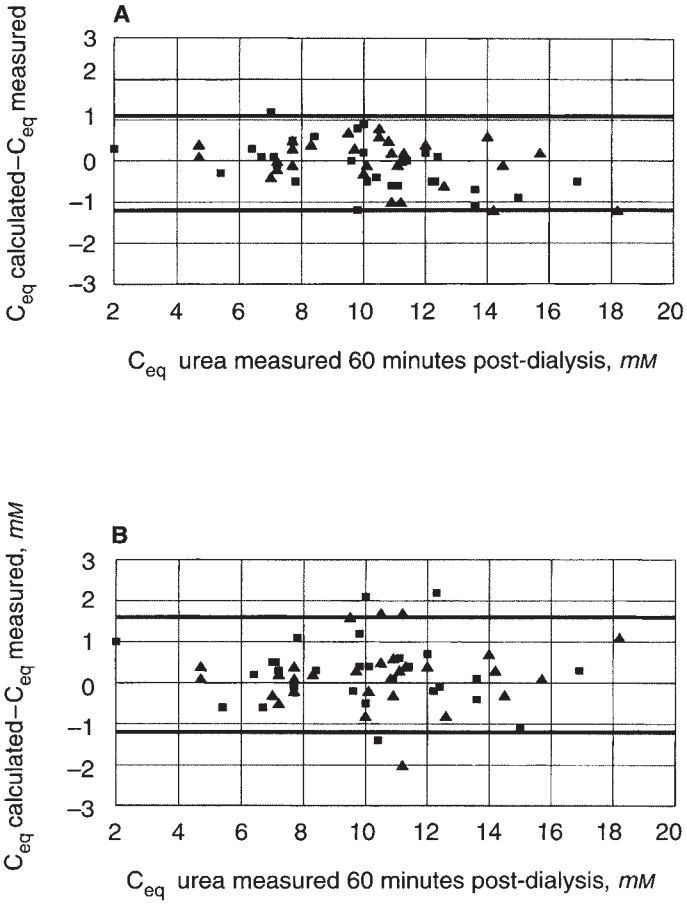

Fig. 5. *Predicting the equilibrated urea concentrations by the tp method (**A**) and Smye method (**B**).* Bland Altman [13] plots representing the difference between calculated and measured C_{eq} urea concentrations in 29 patients after short HDF (triangles) and conventional HD (squares). The solid lines represent mean ± 2 SD.

Rebound prediction

Both the Smye equation and the tp method (using mean tp values) accurately predicted the urea and creatinine rebound (Fig. 5 and Table 2). The Kt/V_{eq} and NPCR calculated using Smye and tp methods agreed with those calculated from the 60-minute post-dialysis sample (Fig. 6 and Tables 3 and 4).

Rebound compensation

The addition of 30 minutes to dialyses prescribed $Kt/V_{sp} = 1$ effectively compensated for the urea rebound in both conventional and short dialyses (Fig. 2 and Table 1). Although the immediate post-dialysis urea concentrations were lower after short HDF than conventional HD, the 60-minute post-dialysis concentrations were similar after allowing for urea generation. Both short HDF and conventional HD had Kt/V_{eq} close to 1. The 30 minute addition was also almost sufficient to compensate for the creatinine rebound.

Table 2. Predicting the urea (in mM) and creatinine (in μM) rebound by different methods in all 58 treatments

	Mean	SE	*P*	*r*	*P*
Urea					
C_{eq} measured *mM*	10.2	ref.			
C_t	8.6	1.6	< 0.001	0.963	< 0.001
C_{eq} predicted by Smye	10.4	0.6	NS	0.969	< 0.001
C_{eq} predicted by tp-35	10.1	0.5	NS	0.983	< 0.001
Creatinine					
C_{eq} *μM*	471	ref.			
C_t	360	102	< 0.001	0.942	< 0.001
C_{eq} predicted by Smye	494	29	< 0.001	0.958	< 0.001
C_{eq} predicted by tp-66	469	12	NS	0.990	< 0.001

Calculation of V

V calculated by the single-pool method varied according to whether urea or creatinine was used as the marker solute and whether C_t or C_{eq} was used as the post-dialysis concentration (Table 5). When V_{sp} was calculated using creatinine C_t, it varied significantly between conventional HD and short HDF. Correction using the tp equations eliminated these differences (Table 5).

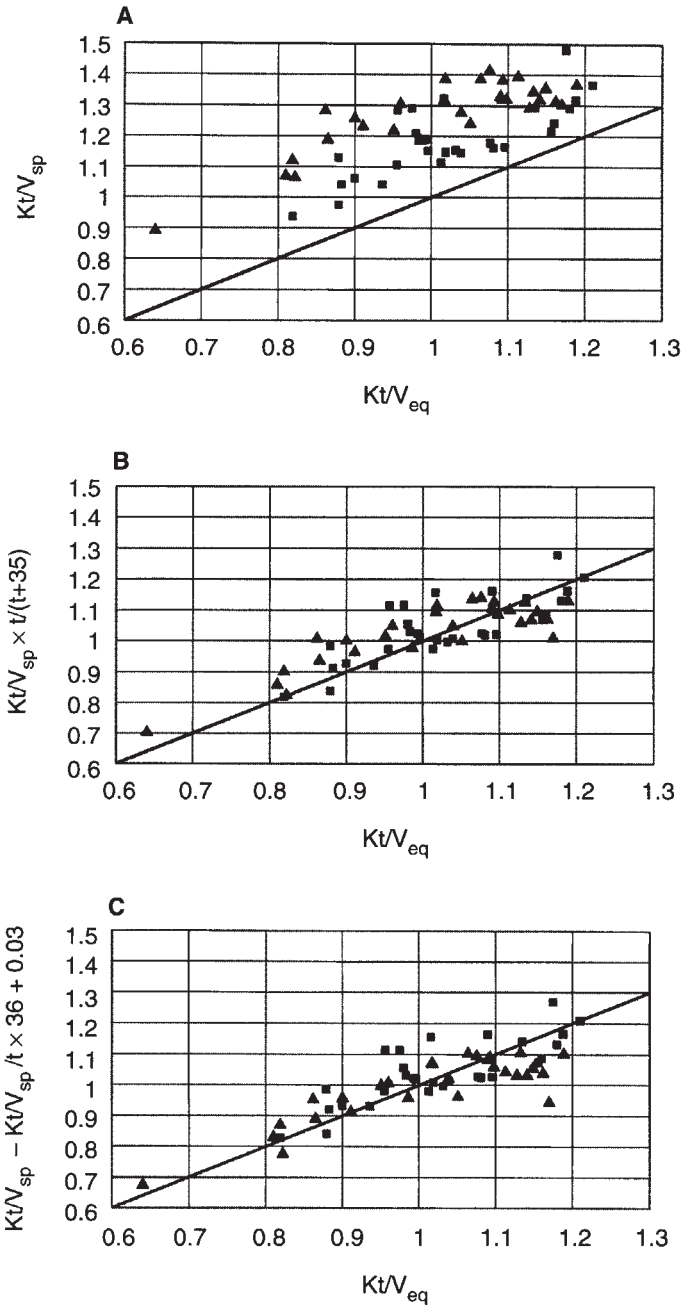

Fig. 6. *Regression plots showing identity lines and symbols as in Figure 5.* Conventional single-pool Kt/V significantly overestimates Kt/V_{eq} (**A**). Predicting urea Kt/V_{eq} by tp method (**B**) or Daugirdas method (**C**) eliminate the systematic error.

Table 3. Predicting Kt/V_{eq} using different methods in all 58 treatments

	mean	SE	*P*	*r*	*P*
Urea					
Kt/V_{eq}	1.062	ref.			
Smye	1.037	0.079	NS	0.752	< 0.001
tp = 35	1.062	0.062	NS	0.856	< 0.001
Daugirdas	1.049	0.064	NS	0.834	< 0.001
Kt/V_{sp}	1.267	0.200	< 0.001	0.744	< 0.001
Creatinine					
Kt/V_{eq}	0.815	ref.			
Smye	0.759	0.074	NS	0.684	< 0.001
tp = 66	0.817	0.035	NS	0.829	< 0.001
Kt/V_{sp}	1.102	0.282	< 0.001	0.620	< 0.001

Table 4. NPCR (in g/kg/day) calculated by different methods in all 58 treatments

	mean	SE	*P*	*r*	*P*
$NPCR_{eq}$	0.970	ref.			
Smye	0.964	0.029	NS	0.977	< 0.001
tp = 35	0.974	0.022	NS	0.991	< 0.001
$NPCR_{sp}$	1.040	0.070	< 0.001	0.985	< 0.001

Table 5. Reproducibility of V (in liters) calculated in conventional HD and short HDF in the same patients by different methods. V_{sp} and V_{eq} were calculated using the conventional immediate post-dialysis sample (C_t) and the post-rebound sample (C_{eq}) as the post-dialysis sample in the single-pool equations

	Conventional HD		Short HDF			
	mean	SD	mean	SD	SE	*P*
Uncorrected						
V_{sp} urea	35.7	6.7	35.4	5.8	2.9	NS
V_{eq} urea	40.9	7.2	44.5	7.0	4.2	< 0.001
V_{sp} creatinine	33.7	6.1	32.1	5.4	3.1	< 0.005
V_{eq} creatinine	43.3	7.4	46.5	6.6	3.9	< 0.001
Corrected						
V_{sp} corr urea	36.3	6.9	36.0	6.1	2.9	NS
V_{eq} corr urea	36.2	6.6	36.5	6.5	2.8	NS
V_{sp} corr creat.	36.3	6.6	35.6	5.9	3.1	
V_{eq} corr creat.	36.3	6.5	35.1	5.8	2.8	NS
V Watson	37.1	5.1	37.1	5.3	0.3	NS

V_{sp} corr and V_{eq} corr were corrected using equations 6 and 7. The mean absolute difference between values calculated during conventional HD and short HDF for each patient are shown (SE). $N = 29$.

The various corrected V values were, on average, 1.2 liters lower than V returned by the Watson equations ($P < 0.001$).

When V was calculated using the six intra-dialytic samples as the post-dialysis concentration ($V_{i1} - V_{i6}$), it was lower than when calculated conventionally: the earlier the sample, the greater the difference. V calculated using C_{eq} (V_{eq}) was significantly higher than when calculated conventionally (Fig. 7 and Table 6). If the tp equations were used to correct V, these differences disappeared except for V_{i1}, using the first intradialytic sample (taken approximately 20 min after the start of dialysis). The tp equation significantly overcompensated for the error in V_{i1} (Fig. 7).

Discussion

Despite prescribing $Kt/V_{eq} = 1$ in these experimental dialyses, the delivered Kt/V_{eq} ranged from 0.65 to 1.21 (Fig. 6). This emphasizes the difficulty in delivering a target Kt/V and the importance of measuring the dose of dialysis actually delivered.

The overestimation of Kt/V caused by the rebound ($Kt/V_{sp} - Kt/V_{eq}$) was similar to those reported by others [6]. In particular, the overestimation of Kt/V was similar to that reported by Daugirdas, and the regression of $Kt/V_{sp} - Kt/V_{eq}$ and K/V was also similar. This overestimation of Kt/V by the single-pool model agrees with those found in studies using direct dialysis quantification [14, 15].

The rebound also affects the calculation of NPCR. By ignoring

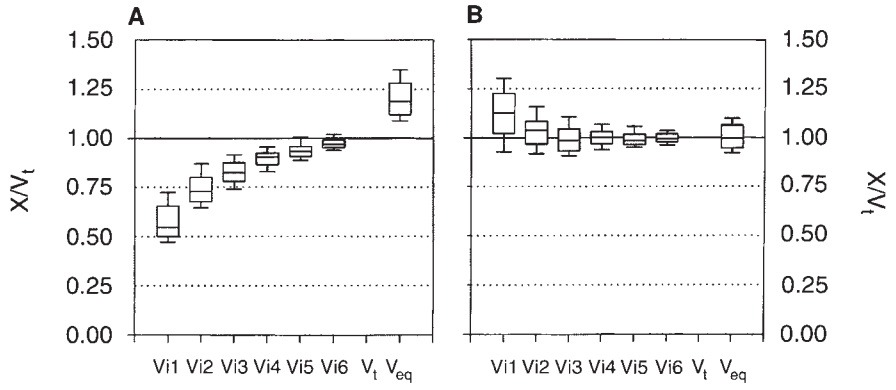

Fig. 7. *The relationship between V_{sp} and delivered Kt/V in 58 dialysis treatments without (A) and with (B) correction using the tp equations.* V_{sp} calculated from 6 intradialytic samples (to mimic low Kt/V) and V_{eq} are shown. V is expressed relative to V_{sp} calculated conventionally from pre- and immediate post-dialysis samples for each treatment. The boxes represent the 10th, 25th, 50th, 75th and 90th centiles.

Table 6. Effect of timing of the post-dialysis sample and marker solute on V with and without correction using the tp equations

	Conventional HD		Short HDF	
	V urea	V creatinine	V urea	V creatinine
Uncorrected				
V_{sp} using C_t	35.7 ref	33.7 ref	35.4 ref	32.1 ref
V_{i5}	34.3 $P < 0.001$	30.6 $P < 0.001$	32.8 $P < 0.001$	28.1 $P < 0.001$
V_{i3}	31.4 $P < 0.001$	25.9 $P < 0.001$	28.3 $P < 0.001$	22.8 $P < 0.001$
V_{eq}	40.9 $P < 0.001$	43.3 $P < 0.001$	44.5 $P < 0.001$	46.5 $P < 0.001$
Corrected				
V_{sp} using C_t	36.3 ref	36.3 ref	36.0 ref	35.6 ref
V_{i5}	36.6 NS	35.7 $P < 0.05$	36.0 NS	35.0 $P < 0.05$
V_{i3}	37.4 $P < 0.05$	35.8 NS	36.2 NS	36.0 NS
V_{eq}	36.2 NS	36.3 NS	36.5 NS	35.1 NS

V_{i5} and V_{i3} are calculated from intra-dialytic samples to represent delivered Kt/V of approximately 0.7 and 0.4. The mean V and probability of it being the same as mean V_{sp} using an immediate post-dialysis sample (C_t) in the same treatment are shown. $N = 29$.

it, the single pool model overestimates the interdialytic rise in urea concentration and NPCR that is calculated from it. Dialysis adequacy is often determined by the position of the pre-dialysis urea plots on a normogram relative to the patient's NPCR. Any NPCR overestimation may shift the patient's plot into the domain defined as representing adequacy. This will tend to mask under-dialysis due to inter-compartment effects. Overestimation of NPCR by the single pool model could partly explain why NPCR measured in hemodialysis patients is generally higher than in CAPD patients [16].

Residual renal function is often calculated from an interdialytic urine collection and the mean interdialytic blood concentration. Blood samples taken immediately post-dialysis at the start of the collection and pre-dialysis at the end of the collection are needed. If the rebound is not taken into account, the mean interdialytic blood concentration will be an underestimate and renal function will be overestimated.

Values of tp were reproducible in the same patients despite being calculated independently from concentrations measured under very different conditions (short HDF and conventional HD). The value tp quantified the rebound in both treatments. This supports the hypothesis that tp is a property of the patient and independent of the dialysis process. The value tp is similar to the 36 minute constant in Daugirdas's equation (equation 2).

The creatinine rebound was significantly greater than the urea rebound. The value tp, describing the time for solute transfer within the patient was almost twice as great for creatinine as urea. Since diffusion is dependent on molecular weight and creatinine has almost double the molecular weight as urea, this suggests that diffusion plays a major part in inter-compartment mass transfer and the post-dialysis rebound. If the rebound is due to regional blood flows as has been suggested [10], than the rebound should not be solute dependent. Uremic toxins of higher molecular weight than creatinine may be important [17]. Extrapolating from the behavior of creatinine, it may be expected that rebound effects would be even greater for these toxins, but more work is needed to investigate this hypothesis.

Values for tp varied significantly between patients. This may reflect quantitative and qualitative differences in cell membranes. Alternatively, it may reflect variability in cardiac index or other patient-related mechanisms such as intra-extracellular osmotic fluid shifts [18], changes in cardiac output or perfusion caused by blood volume changes, cardiac disease or vasoactive drugs.

This inter-patient variation in tp was greater for urea compared to creatinine. This may be because creatinine is more precisely measured in our laboratory. Alternatively, creatinine inter-compartment effects may be more dependent on diffusion due to its greater molecular weight. Diffusion depends on the surface area to volume ratio of the peripheral compartments that should not vary much between patients. Urea inter-compartment transfer is more dependent on flow, which is likely to be more variable.

A mean value of tp could be used to predict the post-dialysis rebound concentration more precisely than the Smye method in the 29 patients studied. Individual variation of the patient's tp contribute to the errors in the tp method for predicting the rebound. The Smye method is not dependent on these patient differences but uses a third sample to calculate the rebound. It seems that the errors introduced by the third sample in the Smye

method are greater than those resulting from inter-patient tp variation. The tp method predicted the urea rebound to within 0.5 mM (1.4 mg/dl) on average. This imprecision is not much greater than the imprecision of the urea measurements themselves.

Although the use of a mean tp value will be a reasonable practical approach and represents an improvement over conventional single-pool analysis, the individual tp variation did significantly impact on both the delivered Kt/V_{eq} and pre-dialysis creatinine in our patients. The patients with the longest tp were relatively underdialyzed and had higher pre-dialysis creatinine concentrations. Further study is needed to determine the variability in tp in a larger number of patients. If there are patients with very prolonged tp (for example those with access recirculation or severe heart failure) assuming a mean value for tp will be inadequate, and it should be measured directly using a 30-minute post-dialysis sample. These uncertainties in the value of tp are relatively more important in short dialysis.

On-line continuous blood solute concentration measurement using an appropriate sensor should allow very precise calculation of tp as a large number of concentrations would be used to compute the log concentration slope. This will allow individual tp variation to be taken into account in the prescription and quantification of dialysis. This approach also allows simple prospective predictions of C_{eq} and C_t by linear projection of the log-slopes.

The value tp was also able to be used to compensate for the urea rebound in the prescription of dialysis time. The addition of 30 minutes per unit of Kt/V prescribed almost completely compensated for the rebound in both conventional and short dialyses. Our results indicate that 35 minutes should have been added for complete compensation. This time increment increases dialysis dose relatively more in short dialyses that also have larger rebounds. Interestingly, the same time increment almost completely corrected the creatinine rebound also despite the tp value being higher for creatinine than urea. This is because creatinine Kt/V_{eq} for the conventional HD was much lower than the urea Kt/V_{eq} due to a combination of lower K and higher rebound. Since the time added is a function of both tp and Kt/V_{eq}, the higher tp is partly canceled out by lower Kt/V_{eq}.

The equations for correcting V_{sp} using tp returned a value of V which was independent of dialysis duration, Kt/V_{eq}, sample timing and marker solute. Although we prescribed $Kt/V_{eq} = 1$ in all treatments, we were able to reproduce the effect of lower Kt/V by calculating V_{sp} using intradialytic samples. The expected error in V_{sp} associated with low delivered Kt/V was corrected by the tp equations.

In theory, the equation should also correct V_{sp} downwards when Kt/V_{eq} is greater than one. Further study employing high delivered Kt/V_{eq} is needed to test this aspect of the correction. The V_{sp} correction equation overcorrected V_{i1}, calculated using a sample taken within the first 20 minutes of dialysis. This is not surprising since the approximations inherent in this approach break down when $t < tp$.

The value for the corrected V was very close to, but significantly lower than the value returned by the Watson formula. This may be because hemodialysis patients are relatively dehydrated at the end of dialysis and have less muscle mass than the normal subjects studied by Watson.

Reported data from the US Renal Data System indicates that hemodialyses deliver on average 28% lower Kt/V than prescribed [19]. Our results suggest that if dialysis is delivered over 150 minutes, Kt/V_{sp} will overestimate Kt/V_{eq} by approximately 20%, partly masking the underdelivery. In the quality assurance of the dialysis process, a 30% shortfall in the delivery of Kt results in a 30% higher than expected V_{sp}. Unfortunately, if delivered Kt/V_{eq} is less than 1, the rebound effects tend to reduce V_{sp} [7], partly opposing the rise in V_{sp} due to the underdelivery of Kt. Our results suggest that if a Kt/V_{sp} of 0.7 is delivered over 150 minutes, V_{sp} will underestimate V by 8%. Appropriate corrections (such as the tp equations) are needed for V_{sp} and Kt/V_{sp} to reveal the true extent of the treatment failure.

The value tp is a clinically convenient method for quantifying inter-compartment transfer in dialysis patients. Unlike other approaches, tp can be calculated directly from time and concentration measurements. It makes no assumptions of the mechanism of the inter-compartment transfer (diffusion or blood flow). No difficult to measure parameter such as V, K, cardiac index or inter-compartment mass transfer rate is needed. We have shown that tp is independent of the rate and duration of dialysis and can be measured reproducibly under different conditions.

Our results suggest that Kt/V_{eq} may be reliably calculated using the tp method without the need for a third or delayed blood sample. The tp correction equations are based on concentration and time measurements only and are therefore unaffected by errors in K or V. The tp method has additional advantages in that it can also be used to compensate for the rebound in the prescription of dialysis time, correct the errors in V returned by single-pool equations, and it can predict the post-rebound concentration for calculation of a rebound-corrected NPCR and residual renal function.

We suggest that hemodialyses are prescribed and monitored using conventional single-pool kinetic modeling but corrected using the tp method. Although value for tp = 35 should be sufficient for most patients, we suggest that tp is measured infrequantly in all patients using a 30-minute post-dialysis sample. If tp is much greater than 35, access recirculation should be suspected. Patients who consistently have high tp values should have this higher value used instead of 35 in the correction equations.

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Appendix

Equation 1. Predicting the equilibrated post-dialysis concentration (C_{eq}) using the Smye method.

$$C_{eq} = C_0 \times \left(\frac{C_t}{C_{int}}\right)^{\frac{t}{t - t_{int}}}$$

Equation 2. The Daugirdas equation for predicting Kt/V_{eq}.

$$Kt/V_{eq} = Kt/V_{sp} - 36 \times \frac{Kt/V_{sp}}{t} + 0.03$$

Equation 3. Calculating tp from concentration measurements only.

$$tp = t \times \frac{\ln\left(\frac{C_{eq}}{C_t}\right)}{\ln\left(\frac{C_0}{C_{eq}}\right)}$$

Equation 4. Predicting the equilibrated post-dialysis concentration (C_{eq}) using the tp method.

$$C_{eq} = C_0 \times \left(\frac{C_t}{C_0}\right)^{\frac{t}{t+tp}}$$

Equation 5. Correcting the error in Kt/V_{sp} using tp.

$$Kt/V_{eq} = Kt/V_{sp} \times \frac{t}{t + tp}$$

Equation 6. Correcting the error in the single-pool V (V_{sp}). The expression $\ln(C_0/C_t)$ is approximately equivalent to Kt/V_{sp}.

$$V = V_{sp} \times \frac{t + tp}{t + tp \times \ln\left(\frac{C_0}{C_t}\right) \times \frac{t}{t + tp}}$$

Equation 7. Correcting the error in the equilibrated V (V_{eq}). The expression $\ln(C_0/C_{eq})$ is approximately equivalent to Kt/V_{eq}.

$$V = V_{eq} \times \frac{t}{t + tp \times \ln\left(\frac{C_0}{C_{eq}}\right)}$$

Equation 8. Prescribing dialysis time, taking the rebound into account.

$$t = \text{desired } Kt/V_{eq} \times \left(\frac{V}{K} + tp\right)$$

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