Equivalent continuous clearances EKR and stdK in incremental haemodialysis

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Abstract
Background. Many haemodialysis patients have residual renal function (RRF), which as such is insufficient to maintain satisfactory quality of life but reduces the demands of treatment and improves outcomes. In incremental dialysis, the dose is adjusted according to RRF, but how should it be done?

Methods. Urea generation rate (G) and distribution volume (V) were determined by the double-pool urea kinetic model in 225 haemodialysis sessions of 30 patients. The effect of different degrees of RRF on equivalent renal urea clearance (EKR), standard urea clearance (stdK) and urea concentrations and required treatment times to achieve the HEMO study standard dose equivalent EKR and stdK targets were studied by computer simulations.

Results. Ignoring RRF leads to underestimation of EKR, stdK, urea generation rate and protein equivalent of nitrogen appearance. Both EKR and stdK increase linearly with renal urea clearance (Kr). The HEMO standard dose equivalent EKRc is 13.8 mL/min/40 L and stdK/V2.29/wk (9.1 mL/min/40 L). The required treatment time to achieve the HEMO-equivalent targets has an almost linear inverse relationship to Kr. If the HEMO standard dose equivalent EKR or stdK is used as the target, RRF may replace several hours of weekly dialysis treatment time. stdK appreciates RRF more than EKR.

Conclusions. RRF is included in the original EKR and stdK concepts. EKR and stdK—determined by kinetic modelling—are promising measures of adequacy in incremental dialysis.

Keywords: computer simulation; EKR; incremental dialysis; residual renal function; stdK/V

Introduction

Patients having residual renal function (RRF) are not a marginal group in the haemodialysis population. In a Dutch study, only 25.5% were anuric at 12 months from beginning of dialysis and 58.1% at 36 months [1].

The renal excretion profile of uraemic solutes is different from that in dialysis. Diuresis helps in managing fluid overload with all of its consequences. RRF lowers predialysis concentrations and reduces the required dialysis dose, diminishing the concentration and volume fluctuations and inconvenience of the treatment.

In the CANUSA study [2], the differences in CAPD outcome were due to differences in RRF [3]. In haemodialysis, RRF correlates positively to outcome [1, 4–10], but early initiation of dialysis [11–23] and extreme attempts to preserve RRF [24–26] are not unequivocally beneficial.

Incremental dialysis [9, 27–32] is a concept of adjusting dialysis dose according to RRF. It was used in 16.5% of patients in the IDEAL study [20]. The most straightforward application of incremental dialysis is a treatment frequency <3/wk used for example by Casino and Lopez [28].

RRF is in effect 168 h per week and may contribute significantly to the total solute removal but only minimally to session Kt/V. Renal function is the reference to which dialysis should be compared. Kt/V, where ‘K’ is defined as dialyser urea clearance, is a measure of a single session and does not permit comparison of different intermittent and continuous treatments and renal function.

Equivalent renal urea clearance (EKR, Casino and Lopez [28]) and standard urea clearance (stdK, Gotch [33, 34]) take the treatment frequency and RRF into account and were intended to be used in comparing dialysis doses in different schedules and to continuous dialysis and renal function. EKR and stdK are based on the definition of clearance (K):

\[ K = E/C. \] (1)

In steady state, the excretion rate equals the generation rate: \( E = G \), so

\[ K = G/C \] (2)

In EKR, C is the time-averaged concentration (TAC) and in stdK, the average pre-dialysis concentration (PAC). stdK
is normalized by dividing the value of equation (2) by the distribution volume \( V \) and expressed usually as weekly \( \text{stdKt/V} \). Dividing \( \text{EKR} \) by \( V \) yields a variable denoted here as \( \text{stdEKR} \). \( G, V, \text{TAC} \) and \( \text{PAC} \) can be determined by kinetic modelling.

\[
\text{EKR} = \frac{G}{\text{TAC}},
\]

\[
\text{stdEKR} = \frac{\text{EKR}}{V},
\]

\[
\text{weekly stdEKR} = \frac{\text{EKR} \times t}{V},
\]

\[
\text{stdK} = \frac{G}{\text{PAC}},
\]

\[
\text{stdK} / V = \frac{\text{stdK}}{V} = \frac{G}{\text{PAC} / V},
\]

\[
\text{weekly stdKt} / V = \frac{\text{stdK} \times t}{V}.
\]

In the above equations, \( t \) is the length of a week. The most practical unit of \( \text{stdEKR} \) and \( \text{stdK} / V \) is \( / \text{wk} \); weekly \( \text{stdEKR} \) and weekly \( \text{stdKt} / V \) are dimensionless. \( \text{stdEKR} \) is always higher than \( \text{stdK} / V \) because \( \text{PAC} > \text{TAC} \). \( \text{PAC} \) has also been called peak average concentration, too [35]. In a symmetric schedule, the peak concentration is equal to the average pre-dialysis concentration. In continuous treatment, \( \text{TAC} \), \( \text{PAC} \) and peak concentrations are equal.

Corrected \( \text{EKR} \) (\( \text{EKRC} \)) is \( \text{stdEKR} \) multiplied by a ‘normal’ distribution volume of 40 L with appropriate unit conversions [28]. The proposed unit of \( \text{EKRC} \) is \( \text{mL/min/} 40 \text{~L} \). It is comparable to a clearance expressed in \( \text{mL/min/1.73m}^2 \), but with a different scaling factor.

\[
\text{EKRC} \left( \frac{\text{mL/min/} 40 \text{~L}}{} \right) = 3.97 \times \text{stdEKR} \left( \frac{1}{\text{wk}} \right).
\]

The total fractional solute removal rate \( (\text{tFURR}) \) of urea is defined here as the amount removed by dialysis and the kidneys during a time unit divided by the average pre-dialysis amount in the body:

\[
\text{tFURR} = \frac{E}{(\text{PAC} \times V)}.
\]

As seen from equations (7) and (10), in a symmetric schedule \( \text{tFURR} = \text{stdK} / V \) if \( E = G \). The most practical unit is \( / \text{wk} \). \( \text{tFURR} \) can be divided into renal fractional solute removal rate \( (\text{rfURR}) \) and dialysis fractional solute removal rate \( (\text{dfURR}) \) components without dialysate collection. The sum of the urea reduction ratios \( (\text{URR}) \) of 1 week’s sessions is a rough approximate of \( \text{dfURR} \).

In the double-pool model, it is not obvious, which concentration should be used as \( \text{TAC} \) and \( \text{PAC} \): whole body water, external pool water or plasma concentration. It is a convention, which has not yet been done. In fractional solute removal rate, the whole body water concentration without converting to plasma concentration must be used and \( \text{tFURR} \neq \text{stdK} / V \).

The European Best Practice Guidelines recommend \( \text{EKR} \) [36] or Solute Removal Index [37] for measuring the dialysis dose in incremental dialysis. Casino and Lopez [28] have created a rough linear regression equation between \( \text{EKRC} \) and \( \text{spKt} / V \), used for example in ref. [38].

The Leyboldt’s weekly \( \text{stdKt} / V \) formula [39, 40], as expressed and recommended in the 2006 DOQI guidelines [41], ignores RRF leading to underestimation of weekly \( \text{stdKt} / V \) if the patient has remarkable RRF. Recently, an improved weekly \( \text{stdKt} / V \) equation taking ultrafiltration (UF) and RRF into account has been published [42] and used in the Frequent Hemodialysis Network (FHN) Trial [43].

The \( a \text{ priori} \) assumption is that renal function is not worse than dialysis with equal urea clearance, but the problem is how to measure urea clearances in intermittent dialysis. This study compares \( \text{EKR} \) and \( \text{stdK} \) as dialysis dose measures when RRF is present.

### Materials and methods

A detailed description of the abbreviations, symbols, definitions and equations is presented in ref. [44].

The data have been gathered by a dialysis information system in the routine care of haemodialysis patients and analysed retrospectively. No randomization, control group or study protocol has been used.

#### Dialysis sessions

The analysis is based on 225 urea kinetic modelling sessions with measurable interdialysis urine volume (Table 1). All the patients were white Europeans.

#### Dialyser clearances

Dialyser clearances are based on 964 \textit{in vivo} blood side clearance measurements. From these, the average blood water \( \text{KoA} \) is calculated for each dialyser model. The actual clearance of each session in this study is calculated from the actual blood and dialysate flow and the dialyser \( \text{KoA} \). In the tables and figures, the ‘dialyser blood water clearance’ means the total (diffusive + convective) clearance used in calculations.

#### Double-pool UKM

Urea kinetic modelling with three blood samples and interdialysis urine collection was done routinely once per month as suggested in the European [37] and American [45] guidelines. Post-dialysis blood samples were taken at the termination of the session with the KDOQI slow-blood-flow

<table>
<thead>
<tr>
<th>Table 1. The current material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>Number of sessions</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Age (Years)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Post-dialysis weight (kg)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>Total body water (L)</td>
</tr>
<tr>
<td>Post-dialysis urea distribution volume</td>
</tr>
<tr>
<td>Urea generation rate (nPNA)</td>
</tr>
<tr>
<td>nPNA (g/kg/day)</td>
</tr>
<tr>
<td>Diuresis (L/day)</td>
</tr>
<tr>
<td>Renal blood water urea clearance (ml/min)</td>
</tr>
<tr>
<td>Renal fractional urea clearancee</td>
</tr>
</tbody>
</table>

aRenal fractional urea clearance (rFC) is renal urea clearance (Kr) divided by urea distribution volume (V) with appropriate unit conversions, sometimes called as “weekly renal Kt/V”. nPNA, normalized Protein equivalent of Nitrogen Appearance.
Equivalent continuous clearances EKR and stdK

In the HEMO study [51], standard dose group average eKt/V was 1.16. To get a safety margin for anuric patients, and due to the bias of the HEMO modification of the Daugirdas rate equation [52], stdEKR and stdK/V values corresponding to eKt/V 1.20 in a conventional 4-h dialysis given three times per week (3 × 4 h/wk) schedule were calculated from 619 modelling sessions (including the 225 of the proper study) as follows:

Single-pool urea distribution volume V1p was calculated for each session with the classic single-pool variable volume urea kinetic model, using Kr determined by the double-pool method. Kd was solved from the Daugirdas eKu/V rate equation:

\[ Kd = (eKu/V - a) \times V_{1p}/(td - b), \]

and 1.20 assigned to eKu/V, 240 min to td and Kd calculated. Dialysis treatment 3 × 4 h/wk was simulated with the double-pool model for each session with this Kd and Kr = 0. stdEKR and stdK/V were calculated. In the HEMO study and in this analysis, a = 0 and b = 24 min. No distinction is made between ANV and AV.

Simulations

The effect of RRF on measures of dialysis dose was studied by simulations based on the double-pool model with the patient-dependent values G and F from the modelling session and varying Kr and treatment parameters, assuming that dialysis has no effect on urea generation and renal urea clearance. The simulations give C0, Ct, TAC, eKu/V, EKR and stdK. With simple computing techniques, one may search for appropriate values of dialysis parameters to achieve a specific stdEKR or stdK/V target.

Statistical methods

Microsoft Excel 2002 software was used in calculating minimum and maximum values and standard deviations and in creating the graphs.

Results

The HEMO-equivalent values of stdEKR and stdK/V were 3.48 /wk and 2.29 /wk, respectively. The stdEKR value corresponds to EKRc 13.8 mL/min/40 L and stdK/V to 9.1 mL/min/40 L.

In the subsequent analysis, only the 225 sessions with measurable RRF were included. The mean renal urea clearance was 1.98 ml/min (0.03–6.32).

The data in Figures 1–6 and in Tables 2–3 are derived from simulations as described in the Materials and methods section. In all figures, the treatment frequency is 3 × /wk and dialyser blood water clearance 187 mL/min to achieve HEMO eKu/V 1.20 in 4 h. In the figures G, V and weekly UF are the average values of the study material (211 µmol/min, 32.6 L and 6.72 L/wk, Tables 1 and 2).

Effect of Kr on measures of RRF and dialysis dose

stdEKR increases in parallel with renal fractional clearance (rFC = Kr/V), stdK/V in parallel with rFURR (Figure 1).

Fig. 1. Effect of Kr on measures of RRF and dialysis dose. Standard dialysis (3 × 4 h/wk, Kd 187 mL/min, HEMO eKu/V 1.20, UF 2.24 L).

Fig. 2. Dependence of required weekly treatment time on RRF. Frequency 3 × /wk, Kd 187 mL/min.
Effect of RRF on the required treatment time

In Tables 2 and 3, the results are calculated individually from $t_d$, $K_d$, $G$, $V$ and $U_F$ of each session and the means of these calculations are presented. The true double-pool $eKt/V$ is shown. It is ~0.05 less than that calculated by the modified Daugirdas rate equation used in the HEMO study. Weekly $eKt/V$ is $eKt/V$ multiplied by treatment frequency individually for each session.

Ignoring RRF does not affect $V$ or $eKt/V$ but lowers considerably $G$, normalized Protein equivalent of Nitrogen Appearance, stdEKR and std$K_t/V$. RRF lowers concentrations and increases stdEKR and std$K_t/V$ (Columns 5 and 3 in Table 2). The treatment time had to be increased by 56 or 123 min per dialysis session to achieve the actual stdEKR or std$K_t/V$, respectively, without RRF.

Because the actual stdEKR and std$K_t/V$ values (Table 2) were substantially greater than the HEMO-equivalent standard dose, simulations with lower dialysis intensity were done to confirm the effect of RRF on the required dialysis time. To achieve the HEMO standard dose equivalent targets, 64 or 123 min more treatment time per session were needed if the patients had had no RRF (Table 3). Of course, in most instances, it had been possible to increase $K_d$ to achieve the target in a shorter time. In this material, the average renal urea clearance 1.98 mL/min corresponds to $0.25–0.36$ units of $eKt/V$.

The average renal urea removal rate is lower with higher dialysis intensity (Column 3 in Table 2 and Columns 3 and 5 in Table 3). Total urea removal rate equals generation rate.

In Figures 2–6, the dialysis dose is varied in an incremental fashion by adjusting the treatment time to achieve the HEMO standard dose equivalent stdEKR and std$K_t/V$ targets.
### Table 2. Required treatment time to achieve the actual stdEKR and stdK/V without RRF

<table>
<thead>
<tr>
<th>Unit</th>
<th>3 Actual</th>
<th>4 Ignored</th>
<th>5 Without</th>
<th>6 stdEKR</th>
<th>7 stdK/V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-dialysis urea distribution volume L</td>
<td>32.6</td>
<td>32.8</td>
<td>32.6</td>
<td>32.6</td>
<td>32.6</td>
</tr>
<tr>
<td>Urea generation rate μmol/min</td>
<td>211</td>
<td>211</td>
<td>211</td>
<td>211</td>
<td>211</td>
</tr>
<tr>
<td>nPNA g/kg/day</td>
<td>1.15</td>
<td>1.02</td>
<td>1.15</td>
<td>1.15</td>
<td>1.15</td>
</tr>
<tr>
<td>Renal blood water urea clearance mL/min</td>
<td>1.98</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Dialyser blood water urea clearance mL/min</td>
<td>199</td>
<td>199</td>
<td>199</td>
<td>199</td>
<td>199</td>
</tr>
<tr>
<td>Dialysis frequency /wk</td>
<td>2.97</td>
<td>2.97</td>
<td>2.97</td>
<td>2.97</td>
<td>2.97</td>
</tr>
<tr>
<td>Dialysis time min</td>
<td>285</td>
<td>285</td>
<td>285</td>
<td>341</td>
<td>408</td>
</tr>
<tr>
<td>Weekly dialysis time h</td>
<td>14.1</td>
<td>14.1</td>
<td>14.1</td>
<td>16.8</td>
<td>19.9</td>
</tr>
<tr>
<td>Ultrafiltration volume L</td>
<td>2.26</td>
<td>2.26</td>
<td>2.26</td>
<td>2.26</td>
<td>2.26</td>
</tr>
<tr>
<td>Weekly ultrafiltration volume L</td>
<td>6.72</td>
<td>6.72</td>
<td>6.72</td>
<td>6.72</td>
<td>6.72</td>
</tr>
<tr>
<td>Pre-dialysis plasma concentration mmol/L</td>
<td>20.8</td>
<td>20.9</td>
<td>24.4</td>
<td>22.2</td>
<td>20.8</td>
</tr>
<tr>
<td>Post-dialysis plasma concentration mmol/L</td>
<td>5.2</td>
<td>5.2</td>
<td>6.1</td>
<td>4.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Time-averaged plasma concentration mmol/L</td>
<td>13.5</td>
<td>13.4</td>
<td>15.6</td>
<td>13.5</td>
<td>12.1</td>
</tr>
<tr>
<td>Time-averaged deviation mmol/L</td>
<td>3.9</td>
<td>3.9</td>
<td>4.6</td>
<td>4.4</td>
<td>4.3</td>
</tr>
<tr>
<td>URR /session</td>
<td>0.75</td>
<td>0.75</td>
<td>0.75</td>
<td>0.80</td>
<td>0.83</td>
</tr>
<tr>
<td>Double-pool eKt/V /wk</td>
<td>2.95</td>
<td>2.95</td>
<td>2.95</td>
<td>2.95</td>
<td>2.95</td>
</tr>
<tr>
<td>Total fractional urea removal rate /wk</td>
<td>2.76</td>
<td>2.38</td>
<td>2.38</td>
<td>2.59</td>
<td>2.76</td>
</tr>
<tr>
<td>Renal urea removal rate μmol/min</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dialysis urea removal rate μmol/min</td>
<td>181</td>
<td>181</td>
<td>211</td>
<td>211</td>
<td>211</td>
</tr>
<tr>
<td>Total urea removal rate μmol/min</td>
<td>211</td>
<td>211</td>
<td>211</td>
<td>211</td>
<td>211</td>
</tr>
<tr>
<td>Renal fraction of urea removal %</td>
<td>13.6</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*The mean actual values of the material are shown in Column 3. Column 4 shows the values calculated by ignoring RRF. Column 5 shows the values if the patients really had had no RRF and they had been dialysed as they actually were. Columns 6 and 7 show the treatment times required to achieve the actual stdEKR and stdK/V with equal dialyser clearances but without RRF. The most important values are in bold. nPNA, normalized Protein equivalent of Nitrogen Appearance.*

### Table 3. Required treatment time to achieve the HEMO-equivalent stdEKR and stdK/V without RRF

<table>
<thead>
<tr>
<th>Unit</th>
<th>3 HEMO stdEKR</th>
<th>4 HEMO stdEKR</th>
<th>5 HEMO stdK/V</th>
<th>6 HEMO stdK/V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal blood water urea clearance mL/min</td>
<td>1.98</td>
<td>0.0</td>
<td>1.98</td>
<td>0.0</td>
</tr>
<tr>
<td>Dialyser blood water urea clearance mL/min</td>
<td>146</td>
<td>146</td>
<td>124</td>
<td>124</td>
</tr>
<tr>
<td>Dialysis frequency /wk</td>
<td>3.00</td>
<td>3.00</td>
<td>3.00</td>
<td>3.00</td>
</tr>
<tr>
<td>Dialysis time min</td>
<td>240</td>
<td>304</td>
<td>240</td>
<td>363</td>
</tr>
<tr>
<td>Weekly dialysis time h</td>
<td>12.0</td>
<td>15.2</td>
<td>12.0</td>
<td>18.2</td>
</tr>
<tr>
<td>Ultrafiltration volume L</td>
<td>2.24</td>
<td>2.24</td>
<td>2.24</td>
<td>2.24</td>
</tr>
<tr>
<td>Weekly ultrafiltration volume L</td>
<td>247</td>
<td>26.5</td>
<td>267</td>
<td>267</td>
</tr>
<tr>
<td>Pre-dialysis plasma concentration mmol/L</td>
<td>10.1</td>
<td>8.9</td>
<td>12.7</td>
<td>9.6</td>
</tr>
<tr>
<td>Time-averaged plasma concentration mmol/L</td>
<td>18.1</td>
<td>18.1</td>
<td>20.4</td>
<td>18.5</td>
</tr>
<tr>
<td>Time-averaged deviation mmol/L</td>
<td>3.7</td>
<td>4.4</td>
<td>3.5</td>
<td>4.3</td>
</tr>
<tr>
<td>Urea reduction ratio /session</td>
<td>0.59</td>
<td>0.66</td>
<td>0.53</td>
<td>0.64</td>
</tr>
<tr>
<td>Double-pool eKt/V /wk</td>
<td>0.90</td>
<td>1.14</td>
<td>0.75</td>
<td>1.11</td>
</tr>
<tr>
<td>Weekly double-pool eKt/V /session</td>
<td>2.69</td>
<td>3.42</td>
<td>2.26</td>
<td>3.33</td>
</tr>
<tr>
<td>stdEKR /wk</td>
<td>3.48</td>
<td>3.48</td>
<td>3.11</td>
<td>3.42</td>
</tr>
<tr>
<td>stdK/V /wk</td>
<td>2.47</td>
<td>2.30</td>
<td>2.29</td>
<td>2.29</td>
</tr>
<tr>
<td>Total fractional urea removal rate /wk</td>
<td>2.30</td>
<td>2.15</td>
<td>2.14</td>
<td>2.14</td>
</tr>
<tr>
<td>Renal urea removal rate μmol/min</td>
<td>40</td>
<td>0</td>
<td>47</td>
<td>0</td>
</tr>
<tr>
<td>Dialysis urea removal rate μmol/min</td>
<td>171</td>
<td>211</td>
<td>164</td>
<td>211</td>
</tr>
<tr>
<td>Total urea removal rate μmol/min</td>
<td>211</td>
<td>211</td>
<td>211</td>
<td>211</td>
</tr>
<tr>
<td>Renal fraction of urea removal %</td>
<td>18.1</td>
<td>0.0</td>
<td>21.1</td>
<td>0.0</td>
</tr>
</tbody>
</table>
In incremental dialysis, with \( Kr = 4 \, \text{mL/min} \), the target stdK/\( V \) is achieved in one half of the time required without RRF. Somewhat longer treatment time is required to achieve the stdEKR target. In both cases, the required treatment time has an almost linear inverse relationship to \( Kr \) (Figure 2).

**Effect of RRF on urea concentrations**

With increasing \( Kr \), dialysing to a constant stdEKR results in decreasing pre-dialysis concentration \( C_0 \) (Figure 3). Dialysing to a constant stdK/\( V \) results in increasing TAC with increasing \( Kr \) (Figure 4). TAD reflects the fluctuation of concentrations. It decreases when \( Kr \) increases with constant stdEKR or stdK/\( V \) (Figure 5).

**Contribution of RRF to urea excretion**

Figure 6 presents the fraction (%) of total urea elimination excreted by the kidneys. With Kr = 4 mL/min, using the HEMO-equivalent stdK/\( V \) as target, almost one half of the total urea excretion takes place through the kidneys. Dialysis and the kidneys interfere with each other and compete for solutes.

**Discussion**

The current analysis is based on the urea kinetic model. One of the parameters in the model is the renal urea clearance (\( Kr \)), which is lower than the glomerular filtration rate. European guidelines [36, 37] suggest glomerular filtration rate as the measure of RRF of dialysis patients, American [41] the urea clearance.

The average kinetic urea distribution volume 32.6 L is 17.5% lower than the anthropometric total body water estimate, only 40% of body mass, but the patients were on the average overweight [body mass index (BMI) 28.8 kg/m\(^2\)]. Daugirdas et al. [53] have observed volume differences of equal magnitude in the HEMO material, where BMI was lower (25.7 kg/m\(^2\)) and kinetically determined volume was 43–44% of body weight.

The HEMO standard dose equivalent stdEKR and stdK/\( V \) values calculated by the double-pool model (3.48 /wk and 2.29 /wk, respectively) are higher than those reported earlier using the single-pool model with equilibrated post-dialysis concentrations (3.34 /wk and 2.23 /wk) [44].

According to urea kinetics, RRF may replace several hours of weekly dialysis treatment time in a conventional three times per week schedule, if HEMO-equivalent stdEKR and stdK/\( V \) values are used as targets. Each mL/min of renal urea clearance corresponds to about 30–60 min of session time in a standard 3 × wk schedule with HEMO-equivalent intensity. Each weekly dialysis hour replaces ~0.7 mL/min of missing renal urea clearance. Other ureaemic solutes may behave differently.

Originally Casino and Lopez [28] held EKRc 11 mL/min/40 L (stdEKR 2.77 /wk) and Gotch [29, 33] stdK/\( V \) 2.0 /wk (7.8 mL/min/40 L) as an adequate dose. Later higher targets were proposed. The HEMO standard dose equivalent stdK/\( V \) 2.29 /wk is equal to 9.1 mL/min/40 L corresponding to an acceptable urea clearance without dialysis. Patients with renal urea clearance of 13.8 mL/min/40 L (stdEKR 3.48 /wk) may have months or even years of satisfactory life left before they begin to benefit from dialysis. Empirically, the optimal stdEKR and stdK/\( V \) values are in conventional haemodialysis considerably higher than in CAPD (HEMO [51], ADEMEX [54]). This discrepancy may have several explanations:

1. the lower TAC in intermittent treatment compensates the drawbacks of concentration and volume fluctuations;
2. the relationship between toxicity and concentration is not linear (the peak concentration hypothesis [55]) and
3. the excretion profile of uremic solutes is different in renal function and CAPD and haemodialysis, i.e. urea is not a good marker solute.

These and other possible factors have been managed in stdK by using a different denominator in the clearance equation (2), making stdK therapeutically ‘more equivalent’ than EKR, which is a ‘mathematically correct’ average clearance.

RRF is inherently included in stdEKR and stdK/\( V \) calculated by the urea kinetic model. RRF lowers especially the pre-dialysis concentrations (denominator in equation (6)) and is included in the UKM formula of \( G \) (numerator in equations (3) and (6); Table 2). Using stdK/\( V \) as the dosing guide in incremental dialysis results in shorter treatment times, lower Kt/\( V \), lower TAD and higher urea concentrations than using EKR (Figures 2–4 and Table 3).

When the dialysis intensity increases, the renal excretion of urea decreases (Table 3, Columns 5 and 3) and when RRF increases, elimination by dialysis decreases (Figure 6). In intermittent dialysis, the average rFURR (/wk) is lower than the renal fractional urea clearance (rFC = Kr/\( V \), /wk) (Figure 1, [42]). dFURR and rFURR depend on each other because both RRF and dialysis affect pre-dialysis concentrations (the denominator) and compete for excretion (the numerator). Total stdK/\( V \) cannot be calculated by adding rFC to stdK/\( V \) calculated with the Leyboldt formula [41] (Figure 1).

Residual renal urea clearance ~4 mL/min/40 L may be the threshold above which concrete short-term benefits may be obtained from incremental dialysis, in the form of a twice per week treatment schedule. It is not far below the threshold above which dialysis is usually not useful. In only 5.5% of all UKM sessions in one centre during 3 years, Kr was >4 mL/min (Vartia A, unpublished). The HEMO standard dose equivalent EKR was not achieved in a 2 × /wk schedule with an average session Kt/\( V \) 1.86 [56]. But many patients appreciate shortening of the session time, too.

In conclusion, if we use systematically stdEKR and stdK/\( V \) as adequacy measures, RRF and treatment frequency will automatically be taken into account. Urea kinetic modelling and a computer are needed in creating the prescriptions. There is in the literature very scanty information about the correlation of stdEKR or stdK/\( V \) to outcome [38, 43] and no studies comparing outcomes in incremental and full-dose approaches. In the FHN trial [43], the average stdK/\( V \) was considerably higher in the frequent haemodialysis group than in the conventional treatment group (3.60 versus 2.57 /wk), but it is difficult to estimate whether the
better outcome was due to the lower concentrations (higher ‘dose’), smaller fluctuation of concentrations and volume, longer weekly treatment time or other factors. Has there been any difference in outcomes, if stdK/V had been equal in both groups? There is no empiric proof showing that equal stdEKR or stdK/V results in equal outcomes in different schedules and with different degrees of RRF, i.e. that they are really universal measures of dialysis adequacy. There is also no data showing which is better as the dosing guide (with different target values), stdEKR or stdK/V, i.e. which correlates more tightly to outcome. stdK/V is more sensitive to RRF and treatment frequency [44, 57] than stdEKR. It is based on the hypothesis that pre-dialysis or peak urea concentrations are important. Using stdK/V as target may lead to high time-averaged urea concentrations and short treatment times, which may hamper water, middle molecule and protein-bound toxin removal. If we apply incremental dialysis, it is important to measure RRF frequently because it may deteriorate unexpectedly.

Conflict of interest statement. None declared.

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Cinacalcet treatment and serum FGF23 levels in haemodialysis patients with secondary hyperparathyroidism

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Abstract

Background. Elevated fibroblast growth factor 23 (FGF23) is associated with adverse clinical outcomes and development of secondary hyperparathyroidism (SHPT) refractory to active vitamin D. Cinacalcet hydrochloride is effective in treating SHPT, but little is known as to whether treatment with cinacalcet alters these levels and whether pretreatment FGF23 levels predict response to this therapy.

Methods. We measured serum full-length FGF23 levels in 55 haemodialysis patients, who participated and completed the 52-week, multicentre, open-label single-arm trial that examined the effectiveness of cinacalcet for treating SHPT.

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