Validation of different methods to calculate $Kt/V$ considering postdialysis rebound

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Abstract

**Background.** The effect of increasing dialysis efficiency magnifies rebound urea and the error in $Kt/V$ determinations from single pool urea kinetics. Several formulae have been developed to calculate $Kt/V$ taking into account the rebound urea ($Kt/V_r$). Smye et al. proposed a method whereby the equilibrated BUN is predicted by an additional intradialytic urea sample ($Kt/V_{rSmye}$). Daugirdas et al. proposed a method based on analysis of post-dialysis urea rebound whereby the $Kt/V_r$ is predicted according to the single pool $Kt/V$ and $K/V$ ($Kt/V_{rDaug}$). Maduell et al. developed a method based on analysis of post-dialysis urea rebound whereby the $Kt/V_r$ is predicted according to the single pool $Kt/V$ and $K/V$ ($Kt/V_{rMad}$).

**Design of the study.** We compared $Kt/V_r$ estimated by these three formulae (Smye, Daugirdas, and Maduell) in 384 patients consisting of 211 males and 173 females, who received dialysis according to their regular protocols. Plasma urea was measured at the beginning, 90–100 min following the start of dialysis, the end, and 45 min post-dialysis.

**Results.** Post-dialysis rebound urea was $22.4 \pm 9.7\%$. $Kt/V$ and $Kt/V_r$ obtained with rea kinetic model $Kt/V = 1.184 \pm 0.22$ and $0.984 \pm 0.20$, respectively. There was a good correlation between $K_t/V_r$ and the Smye formula ($Kt/V_{rSmye} = 0.956 \pm 0.21$, $r = 0.729$, $P < 0.001$), and a better one for Daugirdas ($Kt/V_{rDaug} = 0.984 \pm 0.18$, $r = 0.931$, $P < 0.001$), and Maduell formulae ($Kt/V_{rMad} = 0.980 \pm 0.18$, $r = 0.946$, $P < 0.001$). Limits of agreement and percentage of error estimated according to Bland and Altman show that $Kt/V_r$ estimated by Daugirdas and Maduell formulae could be used in place of the $Kt/V_r$. The degree of agreement with the Smye method is not clinically acceptable.

**Conclusion.** Our results suggest that the use of a single pool $Kt/V$ is not adequate to estimate the haemodialysis dose delivered and $Kt/V_r$ taking rebound urea in consideration. $Kt/V_r$ estimated by Daugirdas or Maduell formulae are a simple and accurate method for use in clinical practice.

**Key words:** $Kt/V$, kinetic urea; rebound urea

Introduction

The adequacy of dialysis has important implications for long-term outcome. Accurate estimation of prescribed and delivered dialysis dose is a central issue in modern dialysis therapy. The effect of increasing dialysis efficiency magnifies rebound urea and leads to overestimation of $Kt/V$ determined from single pool urea kinetics [1]. Several authors have described that rebound urea is related to dialysis efficiency [2,3] and it has been suggested that for short, high-efficiency dialysis treatment, the target $Kt/V$, using single pool urea kinetics, must be increased to ensure adequate therapy [3–5].

In order to calculate $Kt/V$ taking rebound urea into consideration, plasma samples must be obtained 30–60 min after the end of dialysis, which is inconvenient. For this reason, several formulas to calculate an equilibrated $Kt/V$ have been developed. Smye et al. [6,7] have described a formula to calculate an equilibrated end urea, using an additional intradialysis blood sample.

**Table 1.** Observed increase in rebound urea based on dialysis efficiency

<table>
<thead>
<tr>
<th>Dialysis efficiency (Kt/V/h)</th>
<th>Mean K/V</th>
<th>No. patients</th>
<th>Observed rebound urea</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.25</td>
<td>0.23 ± 0.02</td>
<td>15</td>
<td>14.1 ± 4.5</td>
</tr>
<tr>
<td>&lt;0.35</td>
<td>0.31 ± 0.03</td>
<td>157</td>
<td>19.4 ± 8.3</td>
</tr>
<tr>
<td>&gt;0.35</td>
<td>0.44 ± 0.12</td>
<td>227</td>
<td>24.9 ± 9.6</td>
</tr>
<tr>
<td>On-line HDF</td>
<td>0.84 ± 0.14</td>
<td>14</td>
<td>38.1 ± 5.2</td>
</tr>
<tr>
<td>Total</td>
<td>0.38 ± 0.11</td>
<td>284</td>
<td>22.4 ± 9.7</td>
</tr>
</tbody>
</table>

$Kt/V = \ln(C1/C2)$. 

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sample. Daugirdas et al. [8] have proposed a method where a single pool estimate of Kt/V is modified according to the speed of dialysis to obtain a double pool estimate of Kt/V. In a previous report [9], Maduell et al. stated that rebound urea is inversely correlated to urea distribution volume (V), not influenced by dialysis time and directly related to the dialysis efficiency. Through linear regression analysis we developed a formula to calculate Kt/V considering urea rebound according Kt/V, V and K [10,11]. To use this formula it was necessary to have an accurate measure of V through the recollection of dialysate and to make an exact calculation of K. Later, a simpler formula was proposed using K/V in order to avoid failure inaccurate measurement of V and K [12].

The aim of this study was to determine which method provides the most accurate estimate of Kt/V taking rebound urea into consideration and its possible use in clinical practice.

Subjects and methods

The study was carried out on 384 patients, 190 males and 160 females, with a mean age of 60.3 years (range: 20–79 years), regularly treated with haemodialysis at eight different haemodialysis units (Hemogan 62, Gandia Hospital 24, Alcoy Hospital 60, Xativa Hospital 61, Valencia Province Hospital 36, Cedicas 42, Granada Hospital 34, and Castellon Hospital 67 patients).

Each patient received a haemodialysis session according to his or her regular protocol. Residual renal function was not considered. The dialysis parameters were the following: hourly Kt/V, QB 361 ± 72 ml/min (range 200–600); QD 551 ± 107 ml/min (QD 750 or 800 ml/min in 78 patients, 20.3%, and the rest with QD 500 ml/min) and Td 191 ± 27 min. Mean dry weight was 62.7 ± 11 kg. Interdialysis weight increase was 1.93 ± 0.98 kg. Dialyzers were cellulosic in 271 patients (70.6%) and synthetic (polisulphone, polyacrylonitrile) in the rest, with a surface membrane of 1.8 ± 0.18 m² (range: 1.2–2.1 m²). Bicarbonate buffer was used as dialysate in 98% of dialysis sessions. Conventional HD was performed in 223 patients (58.1%) and HDF in 161 patients (41.9%) (HDF of 55 patients were performed with cellulosic membranes, and the rest with synthetic membranes: 81 biofiltration, 10 acetate-free biofiltration (AFB), 2 HDF with paired filtration dialysis (PFD) and 14 HDF with on-line production of substitution fluid.

Blood samples for urea analysis were drawn pre-dialysis (C1), from dry needle tubing after insertion of the needle into the vascular access. Blood flow was slowed to 50 ml/min to take the intradialysis sample (CS) from the arterial line sampling port after 90–100 min of the dialysis session had elapsed. Two post-dialysis samples were taken. The first sample was taken immediately at the end of dialysis (C2) after slowing blood flow to 50 ml/min or by the stopped pump method [13]. Forty-five min after stopping dialysis the last sample was taken (CR) to calculate the following:

Subjects and methods

1. Urea kinetic model Kt/V [14], Kt/V = \ln \left( \frac{C_1}{C_2} \right).
2. Kt/V after rebound urea, Kt/Vr = \ln \left( \frac{C_1}{C_{R}} \right).
3. Estimated Kt/V according to Smye formula [6], Kt/VrSmye = \ln \left( \frac{C_1}{C_{Smye}} \right), where C_{Smye} (the equilibrium postdialysis urea concentration) = C_1 e^{-kT_d} + \frac{C_S}{V} = \ln \left( \frac{C_1}{C_{Smye}} \right), k = 1/(T_d - S) * \ln(C_S/C_F);
4. Kt/V according to Daugirdas formula [8], Kt/V_Daug = \frac{C_1 T_d}{K/V + 0.906}\sqrt{1 - \frac{0.6}{(t/60)}} + 0.03
5. Kt/V according to Maduell formula [12], Kt/V_Mad = \frac{C_1 T_d}{K/V + 0.906}\sqrt{1 - \frac{0.6}{(t/60)}} + 0.03

Kt/V = \ln \left( \frac{C_1}{C_2} \right) is a basic single pool model, but other

Table 2. Statistical comparison between measured Kt/Vr and Kt/Vr estimated by Smye, Daugirdas, and Maduell formulae

<table>
<thead>
<tr>
<th>Kt/Vr</th>
<th>Kt/VrSmye</th>
<th>Kt/VrDaug</th>
<th>Kt/VrMad</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>0.984 ± 0.20</td>
<td>0.956 ± 0.21</td>
<td>0.984 ± 0.18</td>
</tr>
<tr>
<td>r</td>
<td>0.729</td>
<td>0.931</td>
<td>0.946</td>
</tr>
<tr>
<td>Bias</td>
<td>0.0430</td>
<td>0.0006</td>
<td>0.0046</td>
</tr>
<tr>
<td>95% IC</td>
<td>0.026</td>
<td>-0.008</td>
<td>-0.011</td>
</tr>
<tr>
<td>LOA</td>
<td>-0.261</td>
<td>-0.146</td>
<td>-0.120</td>
</tr>
<tr>
<td></td>
<td>0.347</td>
<td>0.146</td>
<td>0.140</td>
</tr>
</tbody>
</table>

IC=Interval of confidence, LOA=limits of agreement.

Table 3. Comparison values of Kt/V, measured Kt/Vr and Kt/Vr estimated by Smye, Daugirdas and Maduell formulae calculated by four different single pool Kt/V methods

<table>
<thead>
<tr>
<th>Kt/V</th>
<th>Kt/Vr</th>
<th>Kt/VrSmye</th>
<th>Kt/VrDaug</th>
<th>Kt/VrMad</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ln(C1/C2)</td>
<td>1.184</td>
<td>0.984</td>
<td>0.956</td>
<td>0.984</td>
</tr>
<tr>
<td></td>
<td>0.0430</td>
<td>0.931</td>
<td>0.946</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.060</td>
<td>-0.008</td>
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</tr>
<tr>
<td></td>
<td>-0.261</td>
<td>-0.146</td>
<td>-0.120</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.347</td>
<td>0.146</td>
<td>0.140</td>
<td></td>
</tr>
<tr>
<td>Daugirdas 2nd generation</td>
<td>1.365</td>
<td>1.140</td>
<td>1.113</td>
<td>1.130</td>
</tr>
<tr>
<td>Basile</td>
<td>1.295</td>
<td>1.139</td>
<td>1.112</td>
<td>1.074</td>
</tr>
<tr>
<td>Jindal</td>
<td>1.547</td>
<td>1.275</td>
<td>1.228</td>
<td>1.276</td>
</tr>
</tbody>
</table>

Kt/V = \ln \left( \frac{C_1}{C_2} \right) is a basic single pool model, but other
methods can be used such as the second generation Daugirdas equation [15]: \( \frac{Kt}{V} = -\ln\left(\frac{C_2}{C_1}\right) - (0.008T) - \left(\frac{UF}{weight}\right) \); or calculation of \( \frac{Kt}{V} \) by related urea reduction ratio formulas (URR). Basile et al. formula [16]: \( \frac{Kt}{V} = 0.23^*URR - 0.284 \), or Jindal et al. formula [17]: \( \frac{Kt}{V} = 0.04^*URR - 1.2 \). These calculations were also determined. Possible definitions of high efficiency dialysis include \( Td < 3 \, h, \, QB > 300 \, ml/min, \, K_{area} > 180 \, ml/min, \, or \, K/V > 5.2 \, ml/min/kg \) [18–20]. In the present study high efficiency dialysis was considered when patients received \( K/V > 0.35/h \) [3]. Data is expressed as mean±standard deviation.
Statistical analysis was performed with a paired Student’s t-test and correlation coefficient were determined. A P value < 0.05 was considered statistically significant. The precision of measured bias was estimated by determining the associated 95% confidence interval (CI). To estimate suitability of interchanging one method with another, limits of agreement (LOA) were determined using the analysis of Bland and Altman [21].

Results

The average postdialysis urea rebound was 22.4 ± 9.7%. High efficiency dialysis (K/V = 0.44 ± 0.12/h) was performed in 227 patients (59.1%), and their rebound urea was 24.9 ± 9.6% and low efficiency dialysis were performed in 157 patients (K/V = 0.31 ± 0.03/h) and the rebound urea was 19.0 ± 8.8% (P < 0.01). Fifteen patients with malfunctioning vascular access or dialysed by central catheters had a K/V < 0.25/h and urea rebound was 14.1 ± 4.5%, and 14 patients with on-line HDF had a K/V > 0.84 ± 0.14 and rebound urea was 38.1 ± 5.2% (Table 1).

The mean value of Kt/V and Kt/Ur was 1.184 ± 0.22 and 0.984 ± 0.20, respectively. Kt/Vr estimated by Smye, Daugirdas, and Maduell formulae were 0.956 ± 0.21, 0.984 ± 0.18, and 0.980 ± 0.18, respectively. The number of Kt/Vr and Kt/UrSmye calculations was 306 (74 intradialysis samples were not drawn) and mean value of Kt/Vr for this pair was 0.999 ± 0.197. The intermethod comparisons between Kt/Vr and Kt/UrSmye showed significant differences (P < 0.001), but no significant differences with Kt/VrDaug nor Kt/VrMad. There was significant correlation between Kt/Vr and Kt/UrSmye, Kt/VrDaug, and Kt/VrMad (Figure 1), although the correlation was weaker for Kt/VrMad, respectively. Limits of agreement for Kt/VrDaug (−0.146 to +0.146) and Kt/VrMad (−0.120 to +0.140) were comparably smaller than those for Kt/UrSmye (−0.261 to +0.347) (Table 2, Figure 2). The limits of agreement indicate a possible error of minus 26% and plus 34% when using Kt/VrSmye instead of the measured Kt/Vr, which is unacceptable from a routine point of view. When Kt/VrDaug is used instead of the measured Kt/Vr, error would fall between −14.6% and +14.6%, and if Kt/VrMad is used, it would be −12% and +14%, which falls into acceptable margins for routine estimation.

High-efficient treatments have been developed over the last years. There have been major improvements in dialysis technology including use of bicarbonate buffer, controlled ultrafiltration, QB ranging 350–500 ml/min, QD ranging 500–1000 ml/min, dialyzers with a KoA between 800–1000 ml/min, and HDF procedures in which diffusion and convection are combined as biofiltration [23,24], high flux haemodiafiltration [25], PFD [26], AFB [27] and on-line HDF [28].

In the present study, 60% of the patients were subjected to high efficiency dialysis and rebound urea was high. In the 1980’s, rebound urea was below 10% and has risen to 10–40% with the use of high efficiency dialysis. In our study, mean rebound urea was 22.4%; which was 25% when K/V > 0.35/h and 19% when K/V < 0.35/h. There were important differences between small group of patients with K/V < 0.25 (rebound urea 14%) and a small group with on-line HDF with K/V > 0.84 (rebound urea 38%). Therefore, if rebound urea is not taken into account, Kt/V is overestimated and its use for monitoring dialysis must be questioned. An accurate estimate of Kt/V would require measurement of urea blood levels 45–60 min after the end of dialysis to give a true equilibrium sample [2]. However, this is inconvenient. For these reasons, methods to calculate an equilibrated Kt/V have been proposed. In the present study, measured Kt/Vr was compared to those estimated by Smye [6], Daugirdas [8], and Maduell [12] formulae. Recently, another formula has been published by Tattersall et al. [29].

The Smye et al. formula [6,7] is the most difficult to use in clinical practice. First, it requires an additional intradialysis sample. This is a disadvantage because the blood flow must be slowed to avoid errors due to access recirculation [30]. Second, this method results in a statistically significant (P < 0.001) difference in estimated value, and the correlation is not so good as the other two methods tested. Finally, limit of agreement and imprecision of estimated bias are excessive. For these reasons we question the use of this formula in clinical practice.

When Kt/Vr, calculated by Daugirdas et al. [8] and Maduell et al. [12] formulas, is compared to the measured Kt/Vr, no statistical differences between methods were observed and there was good correlation. Limits of agreement and imprecision of estimated bias are now acceptable for use in clinical practice. In addition, these formulas are simple and an additional sample is not necessary.

It is recommended that Kt/Vr is used for haemodialysis monitoring. Recent results from the American National Study [31] state that survival benefits from higher dialysis dose appear to be present up to a...
Kt/V (Daugirdas second generation) level of 1.3. In this study, mean dialysis time was 197 min and K/V was 0.328/h. For a Kt/V of 1.3, the estimated Kt/Vr by Daugirdas or Maduell formulae would be 1.09 and it should be a minimum Kt/Vr target. However, Kt/Vr estimated from single pool Kt/V from UKM, Basile and Jindal would be 0.95, 1.05 and 1.20, respectively.

In conclusion, our results suggest that the use of single pool Kt/V is not adequate for estimating delivered haemodialysis dose from high efficiency
treatments and that $K_t/V$ taking urea rebound into consideration should be used. $K_t/V_r$ estimated by Daugirdas or Maduell formulae could be a simple and accurate method for assessing the delivered dialysis dose in clinical practice.

References


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