Urea rebound and delivered Kt/V determination with a continuous urea sensor

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Abstract

Background. The recent introduction of urea sensors for dialysis monitoring has made possible new approaches to urea kinetic modelling. In this study we show how the equilibrated postdialysis urea concentration (C_{eq}) and Kt/V corrected for double-pool urea kinetics (Kt/V_{dp}) can be accurately determined using an on-line sensor providing a continuous measure of blood water urea. A modification of the Smye constant volume double-pool theory led to the following equations for C_{eq} and Kt/V_{dp}:

\[ C_{eq} = C_{pre} \exp(S_{ex} t) \]

\[ B_{dp} = -S_{ex} t + \frac{0 BW}{BW_{dry}} \cdot \frac{3}{1 - 0.0003t} \]

where C_{pre} is the blood concentration measured at the start of dialysis, t is the length of the dialysis session (in min) and S_{ex} is the constant slope of the blood urea logarithm concentration decline following development of the intercompartmental urea concentration gradient in the first 30–60 min of dialysis.

Methods. These equations were tested in 11 patients undergoing 165–240 min of paired filtration dialysis with continuous monitoring of blood urea concentration. C_{pre} was determined as the plateau concentration during a preliminary period of 15–20 min of slow isolated ultrafiltration. S_{ex} was accurately determined from linear regression applied to the urea sensor data from the 80-min point to the end of dialysis.

Results. C_{eq} and Kt/V_{dp} determined from the above equations compared closely to values determined from 25–40 min of urea rebound monitoring with the urea sensor: 10.6 ± 3.0 versus 10.8 ± 2.7 mmol/l (mean ± SD) for C_{eq} and 1.21 ± 0.24 versus 1.18 ± 0.20 for Kt/V_{dp}, compared to single-pool values of Kt/V = 1.34 ± 0.23.

Conclusion. This technique may be readily programmed into on-line urea monitors to provide current and extrapolated values of C_{eq} and Kt/V_{dp} from about the first hour of dialysis.

Key words: haemodialysis; Kt/V; mathematical modeling; rebound; urea kinetic modelling; urea sensor

Introduction

The Kt/V ratio (K = clearance in ml/min, t = length of dialysis duration in min, and V = patient urea distribution volume in ml) has become the universally accepted measure of dialysis dose. Kt/V is most commonly determined from measurements of blood urea concentration predialysis (C_{pre}) and immediately postdialysis (C_{post}). The C_{pre} and C_{post} are substituted into one of several published equations [1–5] to obtain a single-pool value of Kt/V. However, with increased clearances and shortened dialysis times, the validity of single-pool urea kinetics and thus the accuracy of these Kt/V equations come into question. Significant vascular compartment rebound of urea observed in the period immediately following termination of high-efficiency dialysis reflects re-equilibration with body compartments that retained higher urea concentrations during dialysis. The dysequilibrium associated with multiple-pool kinetics suggests that an 'equilibrated' value of urea concentration (C_{eq}), that is the concentration which would be measured if all the urea remaining in the patient at the end of dialysis could be uniformly redistributed throughout V, should replace C_{post} in the two-point Kt/V equation used. A reasonable estimate of C_{eq} can be obtained from a blood sample drawn 30–60 min post-dialysis; however, this approach is impractical as a routine practice. Recently, Smye et al. [6,7] have proposed an equation to predict C_{eq} from C_{pre}, C_{post}, and the urea concentration of an additional blood sample (C_{intra}) obtained 60–80 min into the dialysis session.

There is considerable interest in exploiting urea sensors, which are presently becoming available for haemodialysis monitoring, to automate dialysis urea kinetic modelling, including the necessary corrections.
to account for multiple-pool kinetics. We have been
evaluating for this purpose a urea sensor, the Bellco
UMS (Bellco SpA, Mirandola, Italy), which measures
the blood water urea concentration in the extracorpor-
real arterial stream [8,9]. The objectives of the present
study were:

to adapt the Smye method for use with an on-line
sensor providing a continuous measure of arterial
urea concentration, and
to test the accuracy of estimating C\text{eq} and delivered
Kt/V with this approach in a group of patients in
whom dialysis and postdialytic rebound were
monitored with the Bellco on-line urea sensor.

Theory

The effect of urea dysequilibrium on Kt/V determina-
tion is illustrated in Figure 1. Double-pool urea kinetics
have been simulated for a 70-kg patient (V = 42 litres)
in protein steady state with negligible interdialytic
weight gain, a protein catabolic rate of 1.0 g/kg/day,
and a mass transfer-area coefficient for urea transfer
between intracellular and extracellular pools =
700 ml/min. The patient receives three 3-h dialyses per
week with a dialyser clearance corrected for fistula
recirculation equal to 280 ml/min for a prescribed
Kt/V = 1.20 (= 280 ml/min \times 180 \text{ min} / 42 000 \text{ ml}). For
the midweek dialysis session (see Figure 1) blood urea
concentration (lower broken curve) falls from a pre-
dialysis value of 26.1 mmol/l (C\text{pre}) to 8.4 mmol/l right
at the end of dialysis (C\text{post}). When these predialysis
and postdialysis blood urea concentration values and
t = 180 min are substituted into the following two-
point single pool Kt/V equation [5],

\[
A'B_{dp} = \frac{-\ln A'B_{pre} + 3 \frac{\Delta BW}{BW_{dry}}}{1 - 0.0003t}
\]

(1)

A Kt/V almost equal to the prescribed value of 1.20
is calculated. (\Delta BW represents the excess patient fluid
removed (litres) during the dialysis session and BW\text{dry}
is the patient dry body weight (kg).) However, the
decline in intracellular urea concentration (upper
broken curve of Figure 1) lags behind the extracellular
fall such that the mixed or equilibrated patient urea
concentration (solid curve of Figure 1) at the end of
the dialysis session (C\text{eq}) is 9.9 mmol/l, considerably
greater than the measured blood value, C\text{post} =
8.4 mmol/l. As was mentioned earlier, to compensate
for double-pool urea kinetics, C\text{post} in the single-pool
Kt/V formula must be replaced by C\text{eq}:

\[
A'_{eq} = \frac{-\ln A'_{pre} + 3 \frac{\Delta BW}{BW_{dry}}}{1 - 0.0003t}
\]

(2)

When C\text{eq} = 9.9 mmol/l is substituted into equation 2,
Kt/V\text{dp} is calculated as 1.02. This value represents the

\[
A'_{eq} = \frac{-\ln A'_{eq} + 3 \frac{\Delta BW}{BW_{dry}}}{1 - 0.0003t}
\]

(1)

Fig. 1. Illustration of urea dysequilibrium resulting from double-pool kinetics for a 70-kg simulated patient with PCR = 1.0 g/kg/day, a
prescribed Kt/V = 1.20, and a mass transfer-area coefficient for urea transfer between intracellular and extracellular pools = 700 ml/min.
The upper and lower broken curves correspond to the urea concentration profiles in the intracellular and extracellular compartments
respectively, for a 3-h midweek dialysis followed by 30 min of postdialytic rebound. The solid curve corresponds to the mean urea
concentration in the patient’s total body water.
‘delivered’ Kt/V, the actual quantity of dialysis received by the patient, an amount approximately 15% less than the prescribed Kt/V.

The postdialytic re-equilibration of extracellular and intracellular urea in this patient results in a 19% rebound in blood urea concentration to a value of 10.0 mmol/l 30 min after the end of dialysis. This 30-min postdialytic blood concentration, which slightly exceeds Ceq due to continuing urea generation during the 30 min following termination of dialysis, yields a Kt/Vdp = 1.01 when used as an estimate for Ceq in equation 2.

Although the theory upon which the Smye method [6] for estimation of Ceq is based involves rather complex mathematics it can be readily illustrated graphically. In Figure 2a the urea concentration curves for the patient simulation of Figure 1 have been replotted on logarithmic coordinates. It can be observed that after approximately 60 min of dialysis the extracellular and intracellular urea log concentrations curves fall linearly with nearly the same slope, indicating an exponential fall-off in each compartment concentration after an initial period during which the intercompartmental urea concentration gradient is established. It can also be noted that the mixed or equilibrated patient urea log concentration (solid curve) falls in a nearly linear fashion from the beginning to the end of dialysis with a slope very close to the later portion of the extracellular (or blood) urea log concentration curve. In the Smye method an intradialytic blood urea concentration (Cintra) is measured towards the start of the linear portion of the urea log concentration curve (illustrated in Figure 2a by C80, the urea concentration value 80 min into dialysis). This intradialytic concentration together with the blood urea concentration at the end of dialysis (Cpost) and the time elapsed between the two samples establish the slope of the linear portion of the extracellular urea log concentration curve, S

In the Smye method the slope of the equilibrated patient urea log concentration fall (solid curve, Figure 2a) is assumed to be approximated by S

Thus,

Ceq # Cpre exp(Sex)

This relation is illustrated graphically in Figure 2b, where the extracellular compartment and equilibrated concentration curves now appear as faint lines. The upper heavy solid line represents the Smye approximation to the equilibrated concentration profile. It has been drawn from Cpre with the same slope (Spre) as the lower bold line joining C80 and Cpost. The Smye approximation is seen to slightly overestimate the actual equilibrated concentration, which for this simulated patient has a small downward curvature over the first 30–60 min of dialysis. It does, however, provide a good estimate of the end-dialysis equilibrated urea concentration (10.3 mmol/l) only slightly greater than the actual Ceq (9.9 mmol/l).

An estimate of delivered Kt/V, correcting for two-pool urea kinetics using the Smye theory, can be obtained by replacing Ceq in equation 2 by the right-hand side of equation 5:

When equation 3 is used to replace Spre, equation 7 results:

For the simulated patient of Figures 1 and 2, substitution of C80 = 14.1 mmol/l for Cintra in equation 7 gives a conservative estimate of Kt/Vdp = 0.99.

Equation 7 implies that with the Smye approach only two blood urea concentrations, Cintra and Cpost, are required to determine delivered Kt/V. However, small error in either Cintra or Cpost, inevitable with routine laboratory measurement, can lead to corresponding error in the calculated Kt/Vdp value. The major benefit with on-line monitoring of urea concentration is the quantity of urea concentration data available. For example, the Bellco UMS samples urea concentration every 15 s, providing 400 measurements between the 80-min point and the end of dialysis for a 3-h session. Thus, rather than relying on only two urea concentration values, Cintra and Cpost, to define Sex (equation 3), all the concentration values measured by the sensor from the 80-min point to the end of dialysis can be used to obtain a very accurate value of Sex (by least-squares regression of ln C on t) for more precise calculation of Kt/Vdp with equation 6.

Subjects and methods

The accuracy of Ceq and Kt/Vdp estimation with the Smye method modified for a continuous blood-side urea sensor was tested in a group of 11 stable dialysis patients, seven men and four women, 57.4 ± 17.3 years old (mean ± SD); 73.3 ± 15.6 kg. Each patient underwent a single treatment using the Multimat dialysis system (Bellco SpA, Mirandola, Italy), shown schematically in Figure 3. Sequential convective and diffusive mass transfer or paired filtration dialysis (PFD) is obtained in this system by a haemofilter followed in series by a haemodialyser. Replacement fluid was infused between the two filters (as shown in Figure 3) for eight patients and in the venous bubble trap downstream of the two filters for three patients. The ultrafiltrate stream leaving the haemofilter, which has the same urea concentration as the arterial line blood water entering the haemofilter, passes through the Bellco urea monitoring system (UMS). The UMS consists of conductivity sensors upstream and downstream of a urease
cartridge, which converts all urea in the ultrafiltrate stream into electrolytes. The urea concentration in the ultrafiltrate stream entering the urease cartridge is accurately determined from the rise in conductivity from the first to the second conductivity sensor. The urea concentration profile is displayed on the monitor of a coupled microcomputer which stores the urea concentration measurement every 15 s.

Treatment sessions were divided into three periods. An initial 15–20 min of slow isolated ultrafiltration allowed accurate determination of $C_{\text{pre}}$. This was followed by 165–240...
Urea rebound and delivered \( Kt/V \) determination with a continuous urea sensor

Fig. 3. Schematic of the Bellco paired filtration dialysis system used in this study, including the UMS urea monitoring system which measures urea concentration in the ultrafiltrate drawn from the haemofilter whose composition is equivalent to the urea concentration in the blood water entering the extracorporeal circuit.

min of paired filtration dialysis. Finally, urea rebound was followed for 25–40 min by slow isolated ultrafiltration.

For each treatment the UMS concentration data from the 80-min point into the paired filtration period to its termination were used to obtain \( S_{\text{eq}} \) from least-squares regression of the \( \ln \) concentration values versus time. \( C_{\text{eq}} \) and \( Kt/V_{\text{dp}} \) were determined from \( S_{\text{eq}} \) using equations 5 and 6 respectively. These values were compared with the blood urea concentration measured by the UMS at the end of the rebound phase and the corresponding \( Kt/V_{\text{sp}} \) obtained by substituting the end-rebound concentration for \( C_{\text{eq}} \) in equation 2.

Results

A typical UMS urea concentration trace (patient no. 9) is shown in Figure 4, illustrating the three treatment phases: the 15 min of isolated UF in which measured urea concentration reaches a plateau value \( (C_{\text{pre}}) = 35.2 \text{ mmol/l} \), the 197 min of paired filtration dialysis during which arterial water urea concentration fell to \( 12.6 \pm 3.8 \text{ mmol/l} \) \( (C_{\text{post}}) \), and the postdialytic period showing a 14.0% rebound to 14.3 mmol/l. The PFD and rebound phases of the UMS urea concentration trace have been reproduced on a logarithmic scale in Figure 5. The lower heavy solid line is the linear regression fit to the UMS data from 80 min to the end of the PFD period \( (R^2 = 0.997) \). The parallel heavy solid line drawn from \( C_{\text{pre}} \) is the modified Smye approximation to the patient’s equilibrated urea curve. Extrapolation of this line to the end of PFD yields a predicted \( C_{\text{eq}} = 14.2 \text{ mmol/l} \), very close to the UMS value measured at the rebound plateau \( (14.3 \text{ mmol/l}) \).

Figure 6 shows the excellent agreement between predicted \( C_{\text{eq}} \) determined in this fashion and urea concentration at the end of the rebound phase (mean estimated \( C_{\text{eq}} = 10.6 \pm 3.0 \text{ for all 11 patients versus mean rebound concentration} = 10.8 \pm 2.7 \text{ mmol/l} \)). This may be a reflection of the additional urea generated during the rebound phase. On the other hand the postdialytic monitoring period of 25–40 min may have been too short for complete urea equilibration among body compartments in some patients. We chose not to correct the urea rebound curve for continued urea generation as partial compensation for the shortened postdialytic observation period. In all patients, flattening of the urea rebound trace indicated that urea disequilibrium had been largely dissipated.

The mean urea rebound observed from the postdialytic UMS curve was 15.8 \pm 4.1% when expressed relative to \( C_{\text{post}} \) (i.e., \( [C_{\text{rebound}} - C_{\text{post}}]/[C_{\text{pre}} - C_{\text{post}}] \)) These values compare closely with the corresponding rebound values calculated from the predicted values of \( C_{\text{eq}} \): 12.6 \pm 4.7 and 6.6 \pm 3.4% respectively. The percent rebound values for individual patients are listed in Table 1.

\( Kt/V_{\text{sp}} \) computed from the UMS \( C_{\text{pre}} \) and \( C_{\text{post}} \) values and equation 1 ranged from 0.98 to 1.74 \( \text{mean} \pm \text{SD} = 1.34 \pm 0.23 \). Delivered \( Kt/V \) calculated from equation 2 using the UMS rebound plateau concentration as a measure of \( C_{\text{eq}} \) was about 12% less \( (1.18 \pm 0.20) \) than \( Kt/V_{\text{sp}} \) (see Table 2 for individual patient values and group mean \pm SD). The \( Kt/V_{\text{dp}} \) values were quite well predicted from the UMS PFD trace using the modified Smye method and equation 6 \( (1.21 \pm 0.24) \).

Discussion

The recent introduction of urea sensors for dialysis monitoring makes possible new approaches to urea
Fig. 4. Urea sensor trace recorded for a sample patient (patient no. 9) illustrating the three phases of the study dialysis protocol: 15–20 min of isolated UF to establish $C_{\text{pre}}$; 165–240 min of paired filtration dialysis; and 25–40 min of isolated UF to study postdialytic rebound.

Fig. 5. Urea sensor curve from Figure 4 redrawn on a logarithmic scale. The lower heavy solid line is the linear regression fit to sensor (log) data from 80 min to the end of paired filtration dialysis. A parallel line has been drawn from $C_{\text{pre}}$ to obtain an estimate of the mean urea concentration in the patient’s body water at the end of the dialysis according to the modified Smye approach. The value obtained (14.2 mmol/l) is very close to the rebound plateau value of 14.3 mmol/l.

Kinetic modelling. In this study we show how the equilibrated postdialysis urea concentration and the delivered $Kt/V$ can be accurately determined using a continuous blood-side urea sensor and a modified form of the Smye theory.

The Smye theory [6] is based on a constant volume, double-pool urea kinetic model assuming negligible generation of urea during the dialysis session. According to this model the extracellular compartment urea concentration follows a double exponential fall...
Urea rebound and delivered Kt/V determination with a continuous urea sensor

Fig. 6. Comparison of the estimated value of C\textsubscript{eq} using the modified Smye approach (see Figure 5) with the urea sensor concentration at the end of the monitored rebound period.

Table 1. Percent rebound for individual patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>(C\textsubscript{eq}–C\textsubscript{post})/C\textsubscript{post}</th>
<th>(C\textsubscript{eq}–C\textsubscript{post})/(C\textsubscript{pre}–C\textsubscript{post})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rebound</td>
<td>Predicted</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>1</td>
<td>13.9</td>
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</tr>
<tr>
<td>2</td>
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<td>20.7</td>
</tr>
<tr>
<td>3</td>
<td>14.4</td>
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<tr>
<td>4</td>
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<tr>
<td>Mean</td>
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</tr>
<tr>
<td>SD</td>
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Table 2. Comparison of Kt/V values for individual patients

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<th>Kt/V double pool</th>
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<td></td>
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<td>Predicted</td>
</tr>
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<td>------------------</td>
<td>------------------</td>
</tr>
<tr>
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<tr>
<td>3</td>
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</tr>
<tr>
<td>4</td>
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</tr>
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<td>1.32</td>
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</tr>
<tr>
<td>8</td>
<td>0.98</td>
<td>0.88</td>
</tr>
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</tr>
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<tr>
<td>SD</td>
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</table>

where the first exponential decays much more rapidly than the second. Thus, towards the end of the first hour of dialysis the extracellular (and blood) urea concentration begins to follow a strictly monoexponential decay:

\[ C = B e^{S_{ex} t} \]

This was demonstrated for the simulated patient in Figure 2. It was also found to be the case for each of the patients studied. S\textsubscript{ex}, the decay factor for the monoexponential fall, could be very accurately determined by ln C \textit{versus} t regression analysis applied to the continuous blood urea sensor output from the 80-min mark to the end of dialysis (see Figure 5).

The approximation advanced by Smye \textit{et al.} [6] is that the decline in a patient’s equilibrated urea concentration can be considered monoeponential from the start to the end of dialysis with a decay factor equivalent to S\textsubscript{ex}, the decay factor governing the blood concentration decline after the first hour of dialysis. (This was stated mathematically in the Theory section as equation 5.) It can be shown mathematically that this approximation will always slightly overestimate C\textsubscript{eq} for the constant volume, negligible urea generation case (as in Figure 2b). However, accounting for intradialytic urea generation and ultrafiltration results in a small shift of the theoretical urea concentration curves [10] which may in part cancel the error introduced by the Smye approximation. Our results would indicate this to be the case. We found good agreement between...
C\textsubscript{eq} estimated from the urea sensor trace and urea concentration at the rebound plateau 25–40 min following termination of dialysis (Figure 6). In turn, delivered Kt/V, corrected for the intercompartmental urea gradients which develop during rapid dialysis, could be reliably predicted from the continuous urea sensor output.

In the current study, C\textsubscript{eq} and Kt/V\textsubscript{dp} were determined from a sensor measuring urea concentration of blood entering the paired dialyser. It must be noted that, due to the effects of access and cardiopulmonary recirculation, this urea concentration is slightly lower than the urea concentration in venous blood returning to the heart. However, this does not affect the calculation of Kt/V\textsubscript{dp} as long as recirculation remains unchanged during the treatment session. Other manufacturers have developed [11] or are developing dialysate-side urea monitors [12]. The urea concentration in the spent dialysate is a fixed fraction of arterial urea concentration as long as dialysate flow rate, dialysate clearance, and recirculation rate remain unchanged. Under these circumstances spent dialysate concentration mirrors the fall in arterial urea concentration and the monoexponential decay factor, S\textsubscript{ex}, for calculating Kt/V\textsubscript{dp} from equation 6, can equally well be determined from the dialysate urea profile [13,14]. Dialysate-side urea monitors offer the additional benefit of a direct measure of dialysed urea from which patient protein catabolic rate can be determined [14,15]. In this study we used the 80 min to the end of dialysis portion of the urea sensor curve to determine S\textsubscript{ex} and Kt/V\textsubscript{dp}. However, from examination of Figures 2 and 5 it is clear that with an on-line blood-side (or dialysate-side) sensor providing frequent urea concentration measurements, S\textsubscript{ex} and Kt/V\textsubscript{dp} can be estimated from about 60 min into dialysis. Taking for example the patient of Figures 4 and 5 (patient no. 9), estimating S\textsubscript{ex} from the urea sensor data between 60 and 90 min provides C\textsubscript{eq} and Kt/V\textsubscript{dp} values very close to those determined from the data between 80 min and the end of dialysis [14.4 vs 14.2 mmol/l for C\textsubscript{eq} and 1.11 vs 1.13 for Kt/V\textsubscript{dp}]. Thus it can be anticipated that future versions of on-line urea monitors, using the modified Smye approach illustrated here or more sophisticated urea kinetic modelling software will provide extrapolated values of end dialysis Kt/V\textsubscript{dp} beginning about 1 h into dialysis.

In summary, the Smye technique for estimating postdialytic rebound was modified to take advantage of the large number of concentration data available with an on-line urea sensor. This excess of concentration measurements permits very accurate determination of the decay factor for the monoexponential decline of blood urea concentration which occurs after the inter-

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