Ionic dialysance and the assessment of $Kt/V$: the influence of different estimates of $V$ on method agreement

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Abstract

Background. Ionic dialysance was recently introduced as a means to assess $Kt/V$ ($K_{ID}/V$). With this method, urea distribution volume ($V$) has to be estimated. The primary aim of the present study was to assess the agreement between equilibrated $Kt/V$ assessed by urea kinetic modelling ($eKt/V$) with $K_{ID}/V$ taking into account different estimates of $V$, and to assess the monthly variation in $V$. Secondly, the mechanisms behind the intra-treatment changes in ionic dialysance and inter-treatment variability of $K_{ID}/V$ were assessed.

Methods. Sixty-six patients were included. $eKt/V$ was estimated utilizing 30 min post-treatment sampling in the second generation Daugirdas equation. $V$ was assessed by the formulae of Watson and Chertow ($V_{Watson}$; $V_{Chertow}$), double-pool urea kinetic modelling ($V_{UKM}$) and by ionic dialysance ($V_{IOD}$) [Diascan; Hospal®].

Results. The use of $V_{UKM}$ or $V_{IOD}$ instead of $V_{Watson}$ or $V_{Chertow}$ improved the relation between $eKt/V$ and $K_{ID}/V$ (both $r=0.93$; $P<0.001$ vs. $r=0.84$ and $r=0.81$; $P<0.001$). Mean values of $eKt/V$ (1.19±0.21), $K_{ID}/V_{UKM}$ (1.19±0.30) and $K_{ID}/V_{IOD}$ (1.21±0.25) were comparable. Intra-class correlation coefficient of $V_{IOD}$ was 0.87 with a 1-month interval and <0.75 after 2 and 3 months. Intra-class correlation coefficient of $V_{ID}$ was 0.79 with a 1-month interval and <0.75 after 2 and 3 months. Inter-treatment variation in $K_{ID}/V$ during six consecutive dialysis sessions was 6.1% ± 0.6%. Changes in blood flow were the main determinant of variations in $K_{ID}/V$ ($P<0.05$). During treatment, ionic dialysance decreased by 12±13 ml/min ($P<0.001$). The decline in blood volume was the major determinant of the intra-dialytic change in ionic dialysance ($P<0.05$).

Conclusion. The use of $V_{IOD}$ and $V_{UKM}$ results in better agreement between $eKt/V$ and $K_{ID}/V$ compared with anthropometric formulae. $K_{ID}/V$ was comparable with $eKt/V$ and thus lower than expected for a single-pool method. $V_{IOD}$ and $V_{UKM}$ should be assessed at least monthly. $K_{ID}/V$ varies widely between consecutive dialysis sessions, mainly due to differences in blood flow. During treatment, ionic dialysance decreases, which is related to the relative decline in blood volume.

Keywords: dialysis dose; ionic dialysance; $K_{i}/V$; variability; urea distribution volume

Introduction

An adequate delivery of haemodialysis treatment dose is an important factor in the morbidity and mortality of patients treated with haemodialysis [1]. Regular evaluation of delivered treatment dose, commonly performed by measurement of $Kt/V$, is necessary to intervene when the delivered treatment is inadequate.

To assess $Kt/V$, the second generation Daugirdas formula is advocated by both K-DOQI and EDTA guidelines [2,3]. Both guidelines recommend measurement of haemodialysis dose at least once a month. Recent studies suggest that substantial variation in delivery of $Kt/V$ occurs within intra-individual haemodialysis treatments on a session-to-session basis [4,5]. Thus, a more frequent assessment of $Kt/V$ is desirable. However, the need for blood sampling makes more frequent assessment of $Kt/V$ by the standard approach impractical.

Techniques based on measurement of ionic dialysance facilitate the evaluation of dialysis dose by online monitoring of the $Kt/V$ ($K_{ID}/V$) [6-8]. Assessment of dialysis dose based on ionic dialysance was shown to correlate well with $Kt/V$ assessed by traditional urea kinetic modelling [8,9]. However, despite highly significant correlations, several studies showed either lower or higher values of $K_{ID}/V$ compared with $Kt/V$ assessed by urea kinetic modelling. One reason for these differences is the fact that in some studies,
Ionic dialysance and the assessment of $K_t/V$, which is a single-pool model, was compared with equilibrated $K_t/V$ ($eK_t/V$) [5,8]. However, another factor which is likely to play a major role in the disagreement between $K_{IDT}/V$ and $K_t/V$ assessed by traditional modelling is the estimation of urea distribution volume ($V$). With the ionic dialysance method, $V$ has to be inserted in order to calculate the final $K_{IDT}/V$. So far, in the studies which addressed $K_{IDT}/V$, most commonly the Watson formula is used to assess $V$ ($V_{Watson}$) [8]. However, several studies questioned the reliability of these anthropometry-based equations [4,11].

Assessment of $V$ by urea kinetic modelling ($V_{UKM}$) may be more reliable in this aspect [18]. Recently, an estimate of $V$ with the use of ionic dialysance measurements has been proposed ($V_{IOD}$), which correlated very well with $V$ obtained by direct dialysis quantification and bio-impedance measurements [12,13]. However, a comparison of $V_{IOD}$ with other estimates of $V$ regarding the agreement between $K_t/V$, assessed by urea kinetic modelling and $K_{IDT}/V$ was only assessed in one study in 10 patients [13]. Moreover, the frequency by which $V_{IOD}$ or $V_{UKM}$ would have to be assessed is not known.

Two previous studies showed substantial inter-treatment variations in $K_{IDT}/V$ [5,14]. Although the mechanisms behind these variations remain partly understood, inter-treatment differences in dialysis time and blood flow rate appear to be major determinants [5]. However, until now, only one study has assessed determinants of inter-treatment variations in $K_{IDT}/V$ [5]. One recent study also made apparent that ionic dialysance might change during the dialysis therapy [15]. Although systemic salt loading due to the conductivity measurements might be partly responsible for this phenomenon, also a reduction in clearance per se, e.g. due to fouling of the membrane, might lead to a reduction in ionic dialysance.

The primary aim of the present study was, firstly, to assess the agreement between $K_{IDT}/V$ with $eK_t/V$ taking into account different estimates of $V$.

Secondly, possible mechanisms behind the inter-treatment variability of $K_{IDT}/V$ and intra-treatment changes in ionic dialysance were assessed.

**Patients and methods**

**Patients**

Of our HD patient population, we asked all patients who had been on dialysis for more than three months to participate in the present study. Three patients refused to participate. Sixty-six patients were included in the study.

No changes were made to the dialysis prescriptions over the study period. The study protocol was approved by the local medical ethical committee and informed consent was obtained from each patient. Patient characteristics are displayed in Table 1. In 13 patients, residual renal function was present. Mean GFR in these patients was $2.4 \pm 2.6$ ml/min. Three patients had a central venous catheter. The others were dialysed by either forearm or upper arm fistula or PTFE grafts. Three patients were dialysed twice weekly, the others three times weekly.

**Study protocol**

The agreement between $eK_t/V$ and $K_{IDT}/V$ was assessed after the longest dialysis interval. The inter-treatment variation in $K_{IDT}/V$ (using $V_{Watson}$) was assessed during six consecutive treatments, as was the intra-treatment variation in ionic dialysance. All treatments were monitored for changes in blood flow, relative blood volume, ultrafiltration volume, treatment time, venous pressure, arterial pressure and transmembrane pressure.

**Dialysis strategy**

All but three patients (as mentioned earlier) were treated three times weekly with haemodialysis, using bicarbonate as buffer and a sodium dialysate concentration of 138 mmol/l. Polysulfone (F8HPS; Fresenius) dialysis membranes were used. Target blood flow was 300 ml/min, whereas reached blood flow was $275 \pm 40$ ml/min.

**Urea kinetic modelling**

Pre- and post-dialysis serum urea samples were taken to measure urea reduction at the dialysis session after the longest interval. Post-dialysis blood samples for assessment of $eK_t/V$ were drawn by venipuncture 30 min after the end of dialysis. The $eK_t/V$ was estimated using the second generation Daugirdas equation with the 30 min post-dialytic blood samples added in [2,3]. Also single-pool $K_t/V$ was assessed employing the second generation Daugirdas equation (appendix), using post-dialytic samples drawn 2 min after dialysis.

**Ionic dialysance**

$K_{IDT}/V$ was measured online by Diascan® (Hospal-Gambro®) [6,16]. The calculation of the mean ionic dialysance is based on differences in inlet and outlet conductivity values after a conductivity pulse of 1mS/cm every 30 min. Mean ionic dialysance multiplied by the real duration of the session is used to calculate $K_{IDT}$. $K_{IDT}$ was divided by $V_{Watson}$, $V_{Chertow}$, $V_{UKM}$ and $V_{IOD}$, respectively, to assess agreement with $eK_t/V$.

Determinants of inter-treatment changes in $K_{IDT}/V_{Watson}$ were assessed during six consecutive treatments ($n = 396$). During the same treatments, determinants of intra-treatment variations in ionic dialysance were assessed.
**Urea distribution volume**

$V$ was determined using anthropometrically derived $V$ ($V_{\text{Watson}}$), based on the Watson formula, taking into account post-dialysis weight, height, gender and age [17]. $V$ was also determined using the Chertow formula [18] (appendix).

In addition, $V$ was assessed based on the formula recently proposed by di Filippo et al. taking into account both plasma urea samples and ionic dialysance measurements ($V_{\text{IOD}}$) [12]. Post-dialysis blood samples for assessment of $V_{\text{IOD}}$ and $V_{\text{UKM}}$ were drawn 2 min after the end of dialysis using the slow flow technique [11]. $V_{\text{UKM}}$ was calculated using the calculator available on the HDCN page (http://www.hdcn.com/calcf/dzer.htm). This calculator is based on the two-urea sampling approach as described in [19]. The single-pool volume is corrected for the programme to a double-pool volume as described in [20] (appendix). Variations in the programme to a double-pool volume are determined by an on-line optical method (Hemoscan®, Hospal-Gambro®), assessing relative blood volume changes from blood haemoglobin concentration changes.

**Statistical analysis**

The agreement between data was analysed using Pearson’s $r$ and Bland–Altman analysis [21]. Differences between $eKt/V$ and $K_{\text{ID}}/V$ using the different estimates of $V$ were assessed by the student $t$-test. The standard deviation in $K_{\text{ID}}/V$ and ionic dialysance during the six different treatments were related to the standard deviation of various potential determinants. Multivariate analysis was used to assess determinants of inter-dialytic variation in $K_{\text{ID}}/V$ and intra-treatment changes in ionic dialysance. $P$ values $<0.05$ were considered significant. The variations in $V_{\text{IOD}}$ and $V_{\text{UKM}}$ were also assessed using the coefficient of variation and the intra-class correlation coefficient. An intra-class correlation coefficient $<0.85$ was considered unacceptable for clinical purposes. The SPSS-12.0 package was used for statistical analysis.

**Results**

**Agreement between $K_{\text{ID}}/V$ and $eKt/V$ in relation to different estimates of $V$**

In five patients with inter-dialytic weight gain $<0.1$ kg, the formula for $V_{\text{IOD}}$ yielded unreliable results (NB: in patients with inter-dialytic weight gain $>0.3$ kg, adequate values for $V_{\text{IOD}}$ could be calculated. No patient had inter-dialytic weight gains between 0.1 and 0.3 kg). Therefore, data of 61 patients were analysed.

The $eKt/V$ was $1.19 \pm 0.21$. $K_{\text{ID}}/V$ was $1.12 \pm 0.21$ when corrected for $V_{\text{Watson}}$ ($P < 0.001$ compared with $eKt/V$). $1.00 \pm 0.19$ when corrected for $V_{\text{Chertow}}$ ($P < 0.001$); $1.19 \pm 0.30$ when corrected for $V_{\text{UKM}}$ ($P = \text{ns}$) and $1.21 \pm 0.25$ ($P = \text{ns}$) when corrected for $V_{\text{IOD}}$. Single-pool $Kt/V$, assessed by urea kinetic modeling, was $1.32 \pm 0.31$ ($P < 0.001$).

The correlation between $K_{\text{ID}}/V$ and $eKt/V$ was highly significant ($r = 0.84$ and $r = 0.81$; $P < 0.001$), both when using $V_{\text{Watson}}$ and $V_{\text{Chertow}}$ as an estimate of $V$, although a significant difference between both methods was observed [0.08 ± 0.13; $P < 0.05$] and [0.20 ± 0.13] with wide limits of agreement (Figure 1). Both when using $V_{\text{UKM}}$ and $V_{\text{IOD}}$ as estimates of $V$, the correlation between $K_{\text{ID}}/V$ and $eKt/V$ became stronger (both $r = 0.93$, $P < 0.001$) and limits of agreement were narrower [0.00 ± 0.09] and [−0.01 ± 0.14] (Figures 2 and 3).

**Fig. 1.** Agreement between $eKt/V$ and $K_{\text{ID}}/V$ using $V_{\text{Watson}}$ as estimate of $V$. $eKt/V$: Double-pool $Kt/V$ according to second generation Daugirdas formula; $K_{\text{ID}}/V$: $Kt/V$ assessed by ionic dialysance.

**Fig. 2.** Agreement between $eKt/V$ and $K_{\text{ID}}/V$ using $V_{\text{UKM}}$ as estimate of $V$. $V_{\text{UKM}}$: Urea distribution volume assessed by double-pool urea kinetic modelling.
Monthly variation of V\textsubscript{IOD} and V\textsubscript{DP}

Coefficient of variation of V\textsubscript{IOD} was 15.7% when V\textsubscript{IOD} measurements were compared with a one-month interval, 19.7% when V\textsubscript{IOD} was compared with a two-month, and 15.7% when V\textsubscript{IOD} was compared with a three-month interval.

Intra-class correlation coefficient of V\textsubscript{IOD} was 0.87 when V\textsubscript{IOD} measurements were compared with a one-month interval, 0.68 when V\textsubscript{IOD} was compared with a two-month, and 0.74 when V\textsubscript{IOD} was compared with a three-monthly interval.

Coefficient of variation of V\textsubscript{UKM} was 9.5% when V\textsubscript{UKM} measurements were compared with a one-month interval, 16% when V\textsubscript{UKM} was compared with a two-monthly, and 11.7% when V\textsubscript{UKM} was compared with a three-monthly interval.

Intra-class correlation coefficient of V\textsubscript{UKM} varied from 0.79, 0.73 and 0.57, respectively with a one-, two- and three-monthly interval.

Inter-treatment variation in K\textsubscript{ID}/V and intra-treatment variation in ionic dialysance

Three hundred and ninety-six sessions were studied. Mean coefficient of variation of K\textsubscript{ID}/V between the six measurements was 6.1% ± 4.1% (range 1.3–21.5%). The inter-treatment variation in K\textsubscript{ID}/V is displayed in Figure 4.

With multivariate analysis, the variation in blood flow appeared to be the independent parameter explaining the variation in K\textsubscript{ID}/V (Table 2).

Mean ionic dialysance at the start of dialysance was 170 ± 17 ml/min.

During treatment, ionic dialysance declined by a mean of 11.8 ± 8.9 ml/min (P < 0.001). With multivariate analysis, the intra-treatment change in ionic dialysance was significantly related to the decline in relative blood volume and blood flow rate (Table 3).

Discussion

Our study confirms previous findings [5,6,8–11,22,23] of a good correlation between K\textsubscript{ID}/V and K\textsubscript{t}/V assessed by urea kinetic modelling, but showed significant differences between both methods when anthropometric formulae were used to estimate V. Compared with our study, McIntyre et al. showed a better agreement between K\textsubscript{ID}/V and eK\textsubscript{t}/V with V\textsubscript{Watson} as an estimate of V, but studied a more homogeneous group of patients. We studied an unselected group of dialysis patients, nearly comprising the entire haemodialysis population of a single
When using $V_{UKM}$ or $V_{IOD}$ in the present study, the relation between $eKt/V$ and $K_{IDT}/V$ improved. Mean values of $eKt/V$ and $K_{IDT}/V$ were nearly comparable, despite the fact that $K_{IDT}/V$ is calculated according to a single-pool model. This is in agreement with the results of McIntyre et al. who also showed comparable values between $eKt/V$ and $K_{IDT}/V$, but in contrast to the data of Filippo et al. who showed higher values for $K_{IDT}/V$ compared with $eKt/V$, and to the study of Wuepper et al. where $K_{IDT}/V$ was comparable with single-pool $Kt/V$ [5,12,13]. It has been postulated that ionic dialysance may underestimate effective urea clearance due to the effects of systemic salt loading during the ionic dialysance measurements, resulting in a reduced conductivity diffusion gradient across the dialyser, especially when urea clearance is $>150\text{ml/min}$ [15]. This might explain the fact that $K_{IDT}/V$, both in our study and in the study of McIntyre, was lower than expected for a single-pool model [5].

Differences between the results obtained by Filippo et al. on one hand, and McIntyre and our study on the other hand, could theoretically be explained by lower levels of urea clearance in the former study [5,12]. However, this is unlikely in view of the fact that ionic dialysance in patients studied by Filippo was comparable with our patients [12]. In contrast to most other studies, Wuepper et al. used a model based on a two-step change in conductivity, which has different effects on systemic changes in sodium [13,15]. However, even with a two-step change in conductivity, ionic dialysance may underestimate urea removal [23], which may be related to the effects of cardiopulmonary recirculation [24].

$V_{IOD}$, calculated according to single-pool kinetics, yielded comparable data to $V_{UKM}$, calculated according to double-pool kinetics. This is in agreement with the data of Filippo who showed comparable results between $V$ assessed by direct dialysis quantification (a double pool $V$) and $V_{IOD}$ [12]. It has been shown that with haemodialysis with conventional dose prescriptions the ratio between $V$ assessed by single-pool and double-pool kinetics is nearly one to one [25]. A drawback of our study is the fact that we did not calculate $V$ according to direct dialysis quantification or bio-impedance analysis.

In the small proportion of patients with interdialytic weight gain $<0.1\text{kg}$, calculation of $V_{IOD}$ yielded unreliable values, which may possibly be due to the fact that $V_{IOD}$ was calculated according to single pool variable volume kinetics.

If $V$ is to be assessed by $V_{IOD}$ or $V_{UKM}$, the question arises how often $V$ should be measured. Kloppenburg et al. showed relatively large intra-patient variability in $V$ assessed by urea kinetic modelling [4]. From the data in the present study, the variability in $V_{IOD}$ or $V_{UKM}$ during a one-month period would appear acceptable for clinical purposes, but not when measurements of $V$ are performed with longer time intervals.

In agreement with earlier data of Lambie et al. [14], a significant inter-treatment variation in $K_{IDT}/V$ was observed. In our study, this variation appeared to be mainly related to variations in blood flow rate. Although blood flow rate is routinely prescribed as $300\text{ml/min}$ in our centre, sometimes the blood flow rate had to be decreased in response to changes in venous or arterial pressure, among other reasons, due to needle malpositions. The variations in blood flow rate between treatments are in agreement with the study of Lambie et al. [14]. In our study, changes in treatment time played less of a role compared with the findings of Stewart et al. because treatment time was basically kept unchanged.

In the present study, a decline in ionic dialysance during the dialysis session was observed, which also was described by Gotch et al. [15]. The change in ionic dialysance was related to the change in relative blood volume. The mechanism behind this phenomenon remains to be determined. However, it may be hypothesized that increased clotting of proteins to the dialysers membrane might be involved in less diffusive capacities. In addition, also systemic salt loading due to the conductivity measurements per se might affect measurements of ionic dialysance during dialysis [15]. This phenomenon is especially relevant above a urea clearance of $150\text{ml/min}$ [15] and therefore may also have played a role in the measured changes in the present study. Also, due to the haemoconcentration, the blood water flow rate decreases, resulting in a decline in urea clearance and ionic dialysance during the session.

Concluding, $K_{IDT}/V$ is a useful tool to assess dialysis dose. The use of $V_{IOD}$ and $V_{UKM}$ result in better agreement between $eKt/V$ and $K_{IDT}/V$ compared with anthropometric formulae. $K_{IDT}/V$ was comparable.
Ion dialysis and the assessment of Kt/V with eKt/V, and thus, lower than expected for a single-pool method. Due to the variability in $V_{\text{IOD}}$ and $V_{\text{UKM}}$, these parameters should be assessed at least monthly. $K_{\text{ID}}/V$ varies widely between consecutive dialysis sessions, mainly due to differences in blood flow. During treatment, ion dialysis decreases, which is related to the relative decline in blood volume.

Conflict of interest statement. None declared.

References


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Appendix

Mathematical definitions

$eKt/V$:

$$-LN\left(\frac{C_0}{C_{\text{end}} + 30} - 0.008t\right) + \left(4 - 3.5\frac{C_0}{C_{\text{end}} + 30}\right) \frac{UF}{Wt}$$

Single pool $Kt/V$:

$$-LN\left(\frac{C_0}{C_{\text{end}}} - 0.008t\right) + \left(4 - 3.5\frac{C_0}{C_{\text{end}}}\right) \frac{UF}{Wt}$$

$V_{\text{Watson}}$:

Males: \(2.447 - 0.09516A + 0.1074Ht + 0.3362Wt\)

Females: \(-2.097 + 0.1069Ht + 0.2466Wt\)

$V_{\text{UKM}}$:

$$\frac{FKt}{LN(FC_0/C_{\text{end}})}$$

where

$$F : 1 - 0.44 \frac{K}{V_{SP}}$$

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and

\[ V_{SP} : \quad \frac{Kt}{\ln(C_0/C_{end})} \]

\[ V_{IOD} : \quad \left(\frac{Q_f}{C_0} \right) \left[ 1 - \left( \frac{G - C_{end}(ID - Q_f)}{G - C_0(ID - Q_f)} \right)^{Q_f/(ID - Q_f)} \right]^{-1} \]

where

\[ G (mg/min) : \]

\[ G = \alpha \frac{C_{next} - C_{end}[(V + \alpha \cdot Ti)/V]^{-1}}{1 - [(V + \alpha \cdot Ti)/V]^{-1}} \]

\[ V_{Chertow} : \]

\[ -0.0749A - 1.0178 \cdot male + 0.127 \cdot Ht \]

\[ -0.0401 \cdot Wp + 0.579. \]

\[ diabetes - 0.000672 \cdot Wp^2 - 0.0349 \cdot (A \cdot Wp) \]

\[ + 0.00186 \cdot (Ht \cdot Wp) \]

where

male is equal to 1 for males and 0 for females and diabetes is 1 for diabetics and 0 for non-diabetics.