



Routine assessment of kidney urea clearance, dialysis dose and protein catabolic rate in the once-weekly haemodialysis regimen

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Abstract

Background The dialysis dose (Kt/V) and normalized protein catabolic rate (PCRn) are the most useful indices derived from the urea kinetic model (UKM) in haemodialysis (HD) patients. The kidney urea clearance (Kru) is another important UKM parameter which plays a key role in the prescription of incremental HD. Ideally, the three kinetic parameters should be assessed using the complex software Solute Solver based on the double pool UKM. In the clinical setting, however, the three indices are estimated with simplified formulae. The recently introduced software SPEEDY assembles the aforementioned equations in a plain spreadsheet, to produce quite accurate results of Kru, Kt/V and PCRn. Unfortunately, specific equations to compute Kt/V and PCRn for patients on a once-weekly HD regimen (1HD/wk) were not available at the time SPEEDY was built-up. We devised a new version of SPEEDY (SPEEDY-1) and an even simpler variant (SPEEDY-1S), using two recently published equations for the 1HD/wk schedule. Moreover, we also added a published equation to estimate the equivalent renal clearance (EKR) normalized to urea distribution volume (V) of 35 L (EKR₃₅) from Kru and Kt/V. Aim of the present study was to compare the results obtained using the new methods (SPEEDY-1 and SPEEDY-1S) with those provided by the reference method Solute Solver.

Subjects and methods One hundred historical patients being treated with the once-weekly HD regimen were enrolled. A total of 500 HD sessions associated to the availability of monthly UKM studies were analysed in order to obtain Kru, single pool Kt/V (spKt/V), equilibrated Kt/V (eKt/V), V, PCRn and EKR₃₅ values by using Solute Solver, SPEEDY-1 and SPEEDY-1S.

Results When comparing the paired values of the above UKM parameters, as computed by SPEEDY-1 and Solute Solver, respectively, all differences but one were statistically significant at the one-sample *t*-test; however, the agreement limits at Bland–Altman analysis showed that all differences were negligible. When comparing the paired values of the above UKM parameters, as computed by SPEEDY-1S and Solute Solver, respectively, all differences were statistically significant; however, the agreement limits showed that the differences were negligible as far as Kru, spKt/V and eKt/V are concerned, though much larger regarding V, PCRn and EKR₃₅.

Conclusions We implemented SPEEDY with a new version specific for the once-weekly HD regimen, SPEEDY-1. It provides accurate results and is presently the best alternative to Solute Solver. Using SPEEDY-1S led to a larger difference in PCRn and EKR₃₅, which could be acceptable for clinical practice if SPEEDY-1 is not available.

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Graphic abstract

Routine Assessment of Kidney Urea Clearance (Kru), Dialysis Dose (Kt/V) and Protein Catabolic Rate (PCRn) in the Once-Weekly Haemodialysis (HD) Regimen



• Kru, Kt/V and PCRn are the most useful indices derived from the urea kinetic model (UKM) in HD patients.

• Ideally, the above parameters should be assessed using the complex software Solute Solver¹ based on the double pool UKM.

• The software SPEEDY² simplifies Solute Solver in a spreadsheet and produces accurate results of UKM parameters.

• The following equations^{3,4} to compute single pool Kt/V (spKt/V) and PCRn for the once-weekly HD regimen were not available at the time SPEEDY was built-up:

Eq. 1: $spKt/V = -\ln(R - 0.0035 \times t/60) + (4 - 3.5 R) \times UF/post\text{-dialysis body weight}$
 Eq. 2: $PCRn = -0.46 + 0.01 \times C0 + 0.09 \times eKt/V + 3.94 \times Kru/V$
 where, R = pre-dialysis BUN (C0)/post-dialysis BUN; t = session length, min; UF = ultrafiltration, kg; eKt/V = equilibrated Kt/V; V = urea distribution volume, L.

• Aim of the present study was to devise a new version of SPEEDY (SPEEDY-1) using the new equations for the once-weekly HD regimen.

References: 1. Daugirdas JT et al. *Am J Kidney Dis* 2009; 54: 798–809
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 4. Casino FG et al. *J Nephrol* 2020 doi: 10.1007/s40620-020-00843-9

Conclusions. Our study implemented SPEEDY with a new version specific for the once-weekly HD regimen, SPEEDY-1. It provides accurate results and is the best alternative to Solute Solver.

Methods: SPEEDY-1 computes automatically the following parameters:

1. $Kru = UUN/(C0/0.93) \times UO/1440$, where, UUN = Urinary Urea Nitrogen concentration; UO = Urine Output over the last 24-hour period
2. spKt/V with equation 1; eKt/V = $spKt/V \times t/(t + 30.7)$ (reference 2)
3. Dialyzer urea clearance (K) from KoA and blood flow rate (as detailed in reference 2)
4. Single pool Urea volume (Vsp) = $K \times t/spKt/V$; Vdp from Vsp and eKt/V (reference 2)
5. PCRn with equation 2

Comparison between the paired values of UKM parameters, as computed with SPEEDY-1 and Solute Solver, respectively (500 sessions from 100 historical patients starting on the once-weekly HD regimen).

	Solute Solver	SPEEDY-1	Difference	Agreement*
Kru (mL/min)	5.3 ± 1.8	5.2 ± 1.8	-0.13 ± 0.04	-0.21; +0.05
spKt/V	1.56 ± 0.28	1.55 ± 0.27	-0.01 ± 0.02	-0.05; +0.03
eKt/V	1.38 ± 0.25	1.37 ± 0.24	-0.01 ± 0.02	-0.05; +0.03
PCRn (g/kg/day)	1.04 ± 0.23	1.04 ± 0.27	-0.00 ± 0.07	-0.14; +0.13

Means ± SD; * the agreement limits at the Bland-Altman analysis (mean difference - 2SD and mean difference + 2SD) showed that all differences were negligible.

Keywords Incremental haemodialysis · Kt/V · Once-weekly haemodialysis · Protein catabolic rate · Kidney urea clearance · Urea kinetic modelling

Introduction

The dialysis dose (Kt/V) and the normalized protein catabolic rate (PCRn) are the most useful indices derived from the urea kinetic model (UKM) in haemodialysis (HD) patients [1]. The kidney urea clearance (Kru) is another important UKM parameter which plays a key role in the prescription of incremental HD, starting with a low dialysis dose and a low frequency to be progressively increased to compensate for any subsequent loss in Kru [2]. Ideally, the three kinetic parameters should be assessed using a complex software based on the double pool UKM, as is, for instance, Solute Solver [3], the web-based software recommended by the 2015 KDOQI clinical practice guidelines for HD adequacy [4]. In the routine clinical setting, however, the three indices are currently being estimated with simple formulae, derived from UKM-based studies [5–10]. Recently, a software called SPEEDY has been introduced; it assembles the aforementioned simplified equations in a plain spreadsheet, to automatically produce quite accurate results of Kru, Kt/V and PCRn from a simple input data set [11]. SPEEDY is freely available at www.era-edta.org/en/eudial/ (then click on ongoing projects). Unfortunately, at the time SPEEDY was built, the available equations for estimating Kru and

Kt/V were not specifically devised for patients on the once-weekly HD (1HD/wk) regimen, so that it may not be correct to use these equations with the latter HD regimen. Moreover, an equation estimating PCRn in the once-weekly HD was lacking. In order to fill these gaps, very recently Casino et al. introduced specific equations for Kt/V [12] and PCRn [13].

We devised a new version of SPEEDY (SPEEDY-1) and an even simpler variant (SPEEDY-1S), assembling the above equations to assess Kt/V and PCRn in the once-weekly HD regimen. Moreover, in these versions, we also added a published equation that estimates the equivalent renal clearance (EKR) from Kru, the urea distribution volume (V) and the equilibrated Kt/V (eKt/V) [14].

Aim of the present study was to compare the results obtained using the new methods (SPEEDY-1 and SPEEDY-1S) with those provided by the reference method Solute Solver.

Subjects and methods

Subjects

One hundred historical patients being treated with the once-weekly HD regimen at the Dialysis Centres of San Pedro de

Alcantara Hospital and Virgen del Puerto Hospital, Cáceres, Spain, were enrolled into the study. All patients had given verbal and written informed consent to the choice of HD as first dialysis modality of renal replacement therapy; furthermore, they had accepted to start with the 1HD/wk regimen. Criteria for inclusion in the study were the status of incident patients in the 1HD/wk regimen and the availability of a complete dataset for UKM analysis with Solute Solver. A total of 500 HD sessions associated to the available monthly UKM studies were retrieved from the local electronic clinical databases.

Methods

Kru, single pool Kt/V (spKt/V), eKt/V, V, PCRn and EKR values in the patients on the 1HD/wk regimen were obtained by using three different methods:

Method 1

Solute Solver [3]: it is the reference method and is freely available at www.ureakinetics.org; current version: 2.12, June 4, 2019. Of note, Solute Solver provides EKR values in terms of mL/min. For comparative purposes, the correspondent normalised EKR value was computed as follows: $EKR_{35} = EKR/V * 35$ [14].

Method 2

SPEEDY-1: it is a modified version of the original SPEEDY [11], which is available at www.era-edta.org/en/eudial (ongoing projects). In SPEEDY-1, the equations for estimating Kru, Kt/V, and PCRn have been replaced by slightly modified versions of the original formulae, as shown below:

$$Kru \text{ (mL/min)} = UUN/C0pw \times UO/1440. \quad (1)$$

where, UUN is the urinary urea nitrogen concentration (mg/dL); C0pw (mg/dL) is the pre-dialysis concentration (C0) of Blood Urea Nitrogen (BUN) in the plasma water (i.e., C0 divided by 0.93); UO is the daily urinary output (mL); and 1,440 is the number of minutes in a day. It is a modified version of the Daugirdas [9] and Obi et al. Equations (10), in which the time-averaged concentration (TAC) of urea nitrogen in serum water (TAC-SUNwater) over the urine collection period has been replaced by C0pw.

$$spKt/V = -\ln(R - 0.0035 \times t/60) + (4 - 3.5 \times R) \times UF/BWT. \quad (2)$$

Equation 2 is the “second-generation” equation of the spKt/V introduced by Daugirdas [5], in which the original generation term of 0.008, which refers to the thrice-weekly schedule, has been replaced by the recalculated generation

Table 1 Main data of the patients at the start of the once-weekly HD regimen

Number of patients	100
Gender (male/female)	70/30
Age (years)	69.4 ± 12.4
Height (cm)	165 ± 8
Body weight (kg)	75.6 ± 15.5
Body mass index (kg/m ²)	27.4 ± 5.6
Daily urinary output (mL)	1905 ± 546
Kidney urea clearance (Kru, mL/min)	5.5 ± 2.0

Means ± SD values

Table 2 Main data of 500 dialysis sessions associated to monthly UKM studies

Number of sessions	500
Number of sessions per patient	5.0 ± 4.9
Pre-dialysis body weight (kg)	75.6 ± 14.7
Post-dialysis body weight (kg)	74.2 ± 14.4
Blood flow rate (mL/min)	357 ± 51
Session length (min)	235 ± 16
Pre-dialysis blood urea nitrogen (mg/dL)	79.9 ± 20.6
Post-dialysis blood urea nitrogen (mg/dL)	19.8 ± 6.2
Daily urinary output (mL)	1855 ± 467
Urinary urea nitrogen concentration (mg/dL)	340 ± 91

Means ± SD values

term of 0.0035, which is specific for the once-weekly HD schedule [12]; furthermore, R is the post-dialysis to pre-dialysis BUN ratio; t is the session length (min); UF is the intra-dialysis body weight loss (L); and BWT is the post-dialysis body weight (kg).

$$eKt/V = spKt/V \times (t/(t + 30.7)). \quad (3)$$

Equation 3 is the equation introduced by Tattersall et al. [15], as slightly modified by Daugirdas et al. [3], that estimates eKt/V from spKt/V and the session time, t. Of note, this equation is the one that is already present in the original version of SPEEDY; it was included “as is” in its modified version (SPEEDY-1).

$$ePCRn = -0.46 + 0.01 \times C0 + 0.09 \times eKt/V + 3.94 \times Kru/V. \quad (4)$$

Equation 4 is the recently introduced equation estimating PCRn (ePCRn) [13], absent in SPEEDY, and added in SPEEDY-1. Equation 4 requires the knowledge of V and of the dialyzer urea clearance (K) values. To this end, as detailed elsewhere [11], SPEEDY firstly estimates K from the dialyzer mass transfer-area coefficient for urea (KoA, mL/min), using the same data and equations as Solute Solver does [16]; then it

Table 3 Comparison between the paired values of UKM parameters, as computed by SPEEDY-1 and Solute Solver, respectively (*N* = 500)

	Solute Solver	SPEEDY-1	Difference	P* (2-tailed)	Agreement**
Kru (mL/min)	5.3 ± 1.8	5.2 ± 1.8	− 0.13 ± 0.04	0.00	− 0.21; + 0.05
spKt/V	1.56 ± 0.28	1.55 ± 0.27	− 0.01 ± 0.02	0.00	− 0.05; + 0.03
eKt/V	1.38 ± 0.25	1.37 ± 0.24	− 0.01 ± 0.02	0.00	− 0.05; + 0.03
V (L)	36.6 ± 7.6	36.3 ± 7.4	0.23 ± 0.62	0.00	− 1.01; + 1.48
PCRn (g/kg/day)	1.04 ± 0.23	1.04 ± 0.27	− 0.00 ± 0.07	0.00	− 0.14; + 0.13
EKR ₃₅ (mL/min/35 L)	9.06 ± 1.89	9.10 ± 1.91	0.04 ± 0.39	0.46	− 0.75; + 0.82

Means ± SD

*One-sample t-test.

**Bland–Altman analysis: mean difference ± 2 SD

computes a single pool V (V_{sp}) from the Kt/spKt/V ratio, and finally transforms V_{sp} into a double pool V [17]. SPEEDY-1 does the same as SPEEDY does.

$$EKR_{35} = Kru/V \times 35 + 0.5082 \times (eKt/V)^2 + 3.6195 \times eKt/V - 0.0032. \tag{5}$$

Equation 5 estimates EKR₃₅ from Kru, V and eKt/V [14], as corrected for the typical modelled urea distribution volume (V) of 35 L (EKR₃₅, mL/min/35 L).

The whole sequence of equations in SPEEDY-1 is provided in the Supplementary Material.

Method 3

SPEEDY-1S: it is a simplified version of SPEEDY-1. In fact, as exemplified in the Appendix, it uses only the Eqs. 1–5; furthermore, by assuming that V coincides with the anthropometric estimate of total body water (V_{ant}), as computed by the Watson et al. formula (18), SPEEDY-1S is able to compute ePCRn and EKR₃₅ without all of the complexities associated to the estimates of both K and V, as outlined above.

Statistics

Microsoft Excel 2010 software was used for calculating means and standard deviations (SD), and drawing graphs. All

statistical inferences were made using IBM SPSS Statistics 16.0 (SPSS Inc., Chicago, IL, USA) and values of P < 0.05 were assumed as statistically significant. The Bland–Altman analysis [19] and the one-sample t-test were used when appropriate.

Results

Table 1 shows the main data of the group of 100 patients at the start of the once-weekly HD regimen. On average, data from about 5 HD sessions per patient were available. Table 2 shows the main data of 500 dialysis sessions associated to monthly UKM studies: they were used as input for the subsequent calculations.

Table 3 shows the comparison between the paired values of UKM parameters, as computed by SPEEDY-1 and Solute Solver, respectively. All differences but one were statistically significant at the one-sample t-test; however, the agreement limits at Bland–Altman analysis (mean difference − 2SD and mean difference + 2SD) showed that all differences were negligible: this was true for the two Kru datasets (difference ranging from − 0.21 to − 0.05 mL/min), the two spKt/V datasets (difference ranging from − 0.05 to + 0.03), the two eKt/V datasets (difference ranging from − 0.05 to + 0.03), the two V datasets (difference ranging from − 1.01 to + 1.48

Table 4 Comparison between the paired values of UKM parameters, as computed by SPEEDY-1S and Solute Solver, respectively (*N* = 500)

	Solute Solver	SPEEDY-1S	Difference	P* (2-tailed)	Agreement**
Kru (mL/min)	5.3 ± 1.8	5.2 ± 1.8	− 0.13 ± 0.04	0.00	− 0.21; + 0.05
spKt/V	1.56 ± 0.28	1.55 ± 0.27	− 0.01 ± 0.02	0.00	− 0.05; + 0.03
eKt/V	1.38 ± 0.25	1.37 ± 0.24	− 0.01 ± 0.02	0.00	− 0.05; + 0.03
V (L)	36.6 ± 7.6	36.8 ± 5.8	0.72 ± 5.28	0.00	− 9.83; + 11.28
PCRn (g/kg/day)	1.04 ± 0.23	1.02 ± 0.25	− 0.02 ± 0.12	0.00	− 0.26; + 0.22
EKR ₃₅ (mL/min/35 L)	9.06 ± 1.89	8.96 ± 1.76	0.10 ± 0.87	0.00	− 1.85; + 1.65

Means ± SD;

*One-sample t-test

**Bland–Altman analysis: mean difference ± 2 SD

L), the two PCR_n datasets (difference ranging from -0.14 to $+0.13$ g/kg/day), and the two EKR₃₅ datasets (differences ranging from -0.75 to $+0.82$ mL/min/35 L).

Table 4 shows the comparison between the paired values of UKM parameters, as computed by SPEEDY-1S and Solute Solver, respectively. Of note, the results concerning Kru, spKt/V and eKt/V were the same as those shown in Table 3, the same formulae and the same data being used. However, the agreement limits at Bland–Altman analysis between the Vant and the double pool V values were relatively good: in fact, the SDs were quite large, so that the individual differences ranged from -9.83 to $+11.28$ L. Similarly, the agreement limits at Bland–Altman analysis between the PCR_n and EKR₃₅ values computed using the Vant and the corresponding ones obtained with Solute Solver were relatively good, their difference ranging from -0.26 to $+0.22$ g/kg/day and from -1.85 to $+1.65$ mL/min/35 L, respectively.

A list of abbreviations is provided in the Supplementary Material.

Discussion

Until recently, no simplified formulae were available for the routine assessment of Kru, Kt/V and PCR_n in the once-weekly HD regimen. This was likely due to the fact that this regimen was rarely prescribed in the past and usually for short time periods in the early phase of the renal replacement therapy. On the contrary, nowadays there is an increasing interest in an incremental approach to HD, be it with one or two sessions per week [20–23]. As a matter of fact, a recent meta-analysis of cohort studies concluded that incremental dialysis “allows longer preservation of residual kidney function (RKF) thus deferring full-dose dialysis by about 1 year in HD and PD, with no increase in mortality risk” [24]. No randomized clinical trials testing incremental HD have yet been published [25]. Actually, one clinical trial, named IHDIP, is ongoing [26] and another one, named REAL LIFE, is starting patient enrolment [27]. Interestingly, both trials base the prescription of the once-weekly HD regimen on the recently introduced “Variable Target Model” (VTM) [14]. At variance with the so called “Fixed Target Model” (FTM), using VTM allows a lower dialysis dose and a lower Kru with respect to the current concepts of dialysis adequacy in incremental HD [14]. In short, FTM assumes that adequacy in incremental HD requires that the sum of dialysis clearance and kidney clearance be constant. One could easily realise that this is a wrong assumption by simply considering that, if it is only the sum of dialysis clearance and kidney clearance that matters, at the extremes, it should be indifferent if the given total clearance were obtained only by the native kidneys (patient not yet on

dialysis) or only by dialysis (dialysis patient in anuria). To try to correct, at least in part, the mistakes derived by using a “fixed” target for the total clearance, Casino and Basile suggested using a “variable” target [14]. In short, by expressing the total (kidney + dialytic) clearance in terms of EKR, they hypothesized that the adequate EKR could vary from a minimum, at a selected Kru threshold to start HD, to a maximum corresponding to the selected adequate dialysis dose in the anuric state [14]. In conclusion, basing adequacy on VTM could allow to prescribe the 1HD/wk regimen in patients whose Kru is comprised between 5 and 3 mL/min/35 L, with a delivered spKt/V of about 1.2 [27]. Of note, neither trial [26, 27] requires the formal prescription of a strict low-protein diet to start and maintain incremental HD, essentially because, even if a low-protein diet could very likely help to preserve RKF, its mandatory prescription would drastically reduce the number of patients that could be offered the incremental approach. In fact, an important study focusing on a Combined Diet Dialysis Program concluded that “a low-protein diet combined with weekly hemodialysis can be considered only in motivated and selected ESRD patients” [21]. On the contrary, our hypothesis is that an infrequent HD schedule is the main factor that can help to preserve RKF: here, it must be stressed that the *conditio sine qua non* of the prescription of the once-weekly HD regimen is very strict monitoring of both RKF [23] and of the clinical status of the patients with a timely increase in the dose and/or frequency of treatment if needed [26, 27]. Clearly, the results of the two trials will confirm or reject their underlying hypotheses, including, among others, not only the validity of VTM but also the possibility of prescribing the 1HD/wk regimen to patients with preserved Kru without a strict low-protein diet [26, 27].

In any case, selected adequacy targets apart, the availability of simplified formulae to compute Kru, Kt/V and PCR_n for patients in the 1HD/wk regimen could favour further studies on this issue. As stated above, two such equations have been introduced and validated to estimate spKt/V [12] and PCR_n [13], respectively. The latter equations have been introduced into the new version of SPEEDY, SPEEDY-1. Moreover, we also tested a simple formula (Eq. 1) to assess Kru, based on the hypothesis that the well known slow increment in BUN over the last 24 h prior to the weekly HD session could allow using the pre-dialysis BUN, in terms of plasma water concentration, as a proxy for the TAC-SUN-water [9, 10] over the urine collection time period.

To summarize: we improved the original version of SPEEDY [11], by replacing the old equations estimating Kru and spKt/V with Eqs. 1 and 2, respectively, and adding two formulae for estimating PCR_n and EKR₃₅, respectively. This modified version, SPEEDY-1, provides accurate results and is the best alternative to Solute Solver as shown in Table 3.

However, it is relatively complex because it has to estimate K and V. Thus, we tested a simplified version of SPEEDY-1, SPEEDY-1S: actually, we tested whether using Vant, that avoids the assessment of K and V, could provide acceptable PCRn results, in spite of the well known fact that Vant can markedly overestimate V [28]. As shown in Table 4, using Vant led to a difference in PCRn ranging from -0.26 to $+0.22$ g/kg/day, quite an important difference corresponding to -25% and $+21\%$, respectively.

In conclusion, we implemented SPEEDY with a new version that is specific for the once-weekly HD regimen, SPEEDY-1. It provides accurate results and is the best alternative to Solute Solver. Using Vant instead of V in SPEEDY-1S led to a larger difference in PCRn and EKR_{35} , which could be acceptable in clinical practice if SPEEDY-1 is not available.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40620-021-01033-x>.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Research involving human participants and/or animals This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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