COMMENTARY

Normalization of Dialysis Dose for Daily Dialysis

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The equilibrated Kt/V (eKtV) is widely used in hemodialysis (HD) as a measure of the intensity (magnitude) of an individual dialysis treatment. Adequate eKt/V for thrice-weekly hemodialysis (twHD) has been extensively studied, and a value in the range 1.0 – 1.1 per treatment (3.0 – 3.3 weekly) is generally considered to represent adequate therapy for this specific frequency of dialysis. However, for other schedules, summing eKt/V's and time-averaging the clearance is not appropriate. This was first demonstrated several years ago by the observation that a weekly eKt/V of 2.0 in continuous ambulatory peritoneal dialysis (CAPD) is therapeutically equal to a weekly eKt/V of 3.0 in twHD. That paradox has been resolved by the standard Kt/V (stdKt/V), which accounts for the first order nature of solute removal by dialysis, and which correctly predicts a normalized weekly stdKt/V of 2.0 for both CAPD and twHD.

The equivalent renal clearance (EKR) has also been advanced as a method to normalize dose for varying treatment schedules. However, mathematical consideration shows that EKR is an exact time-averaged clearance. Analysis of data reported for daily dialysis by Piccoli et al. *in the present issue of* Hemodialysis International *shows that the* $EKR_c\ t/V$ *calculated for daily dialysis is identical to the sum of eKt/V's for the individual dialyses. We therefore conclude that EKR is not a suitable parameter for normalizing the dialysis dose, because it fails to reflect the effect of dialysis frequency in HD therapy.*

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Key words

Daily hemodialysis, kinetics, urea, adequacy

Introduction

The report by Piccoli and colleagues in this issue [1] on monitoring dosage in daily dialysis addresses a very timely concern. They evaluated several different methods of dose calculation, with the primary purpose of determining the optimal way to minimize variability in the measurement of the total delivered dose with 6 treatments per week. Their report provides valuable guidelines for monitoring dose in daily dialysis. However, the interrelationships among the methods of dose calculation are also of considerable interest and are the subject of this commentary.

The spectrum of dialysis treatment has been greatly expanded over the past few years. Clinical therapy now encompasses (a) continuous ambulatory peritoneal dialysis (CAPD), (b) CAPD combined with 1 or 2 hemodialysis (HD) sessions per week, and (c) intermittent hemodialysis with a wide range of frequencies (3 – 6 times per week) and intensities (2 hours to 8 hours nocturnal). A normalized dose parameter suitable for quantitative comparison of dialysis dose across this wide spectrum of therapy is needed.

The concept of Kt/V was developed from thrice-weekly HD (twHD) therapy [2]. Adequate twHD was subsequently shown to require a minimum equilibrated Kt/V (eKt/V) of 1.05 (equivalent to a single-pool Kt/V of 1.2 – 1.5, depending on t) to be given during each of the three weekly dialyses [3]. Although this dose parameter has been validated only for twHD, the dose provided with more frequent dialysis is now often described as the sum of individual eKt/V values over a week (ΣeKt/V) and is compared to ΣeKt/V for twHD.

Solute removal by dialysis is first order—that is, the rate of solute removal (J) equals concentration (C) times clearance (K). Dialysis efficiency (J) therefore falls sharply as the dose of each dialysis (Kt/V, intensity) increases, owing to the fall in C. Doubling the frequency at the same Kt/V results in a much greater increase in total dose than does doubling the intensity, Kt/V, at the same frequency. Consequently, it is not appropriate to use the ΣKt/V to compare doses under varying treatment schedules. Implicit in the weekly ΣKt/V calculation is the assumption that the total clearance provided by any therapy schedule can be time averaged (TAK) regardless of the frequency of dialysis. That is,

$$TAK = (\Sigma Kt/V)\ (V)\ /\ T \qquad (1)$$

where T is the total averaging time (typically 1 week). Neither TAK nor ΣKt/V are appropriate measures to compare the

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amount of therapy delivered under varying schedules. For example, they would not distinguish between 3 dialyses per week with each Kt/V being 2.0 and 6 dialyses per week with each Kt/V being 1.0. The ΣKt/V is 6.0 in each case, but the 6-times-weekly schedule is far more efficient owing to a two-fold increase in frequency.

A rational method for modeling a "standardized" dose (stdKt/V) for all treatment schedules by accounting for the first order nature of solute removal has been reported [4,5]. The stdK is an equivalent continuous clearance calculated from the urea nitrogen generation rate (G) and the mean pre-dialysis urea nitrogen concentration (mCo) in accordance with

$$\text{stdK} = G / \text{mCo} \qquad (2)$$

and the stdKt/V is

$$\text{stdKt/V} = [\,\text{stdK}\,(7)\,(1440)\,/\,N\,]\,/\,V \qquad (3)$$

where N is number of dialyses per week, and V is urea distribution volume. The stdK is a kinetically defined continuous clearance, which is thought suitable to quantify the total HD dose for any treatment schedule (that is, any frequency and intensity). It has been shown to correctly predict doses required for adequate therapy in both CAPD and twHD, but to date it has not been clinically evaluated for other therapies, such as daily dialysis.

Another dosage model, the "equivalent renal clearance" (EKR), has been reported by Casino and Lopez and is also considered to be suitable for dose normalization in all treatment schedules [6,7]. The model considers the EKR to be a steady-state continuous clearance, therapeutically equivalent to the total clearance provided by any treatment schedule. It is defined as

$$\text{EKR} = G / \text{TAC} \qquad (4)$$

and

$$\text{EKR}_c\text{t/V} = [\,\text{EKR}\,(7)\,(1440)\,/\,N\,]\,/\,40 \qquad (5)$$

where G is the urea nitrogen generation rate, TAC is the time-averaged urea nitrogen concentration over a full week of treatment, N is number of dialyses per week, and 40 is the standard volume normalization parameter chosen by Casino.

The kinetic meaning of EKR can best be seen from the steady-state relationship between G, TAC, and TAK

$$G = \text{TAK}\,(\,\text{TAC}\,) \qquad (6)$$

which can be rearranged to give

$$\text{TAK} = G / \text{TAC} \qquad (7)$$

A comparison of equations (4) and (7) shows that EKR = TAK, and that ERK defines total dose simply as the sum of the Kt/V values regardless of treatment schedule. The EKR does not account for the first order nature of solute removal.

The clinical data reported by Piccoli and colleagues [1] provide an opportunity to examine this assessment of EKR. That group calculated and reported the single-pool variable volume Kt/V value for each session (Kt/V per session) using the Daugirdas approximation formula [8]. They also calculated the EKR_c from each session's data using Casino's plots [6,7].

Equation (5) was used to calculate mean EKR_c(t)/V for each patient from the mean EKR_c and t values reported for each patient. The EKRc(t)/V was computed both per session and per week.

The Kt/V(Daugirdas) values for each session are 0.65 – 0.97 and are in a range where V is systematically underestimated and Kt/V is systematically overestimated. Therefore, the Kt/V(Daugirdas) values were corrected for this effect (corrKt/VDaug per session), using the Tattersall algorithm for correction of volume error [9],

$$\text{corrKt/VDaug} = [\,\text{Kt/VDaug}\,] \times [\,\{\,t + tp\,(\,\text{Kt/VDaug}\,)[\,t\,/\,(\,t + tp\,)]\,\}\,/\,(\,t + tp\,)\,] \qquad (8)$$

where tp is patient equilibration time (35 minutes).

Table I lists the Kt/V(Daugirdas), corrKt/VDaug, and calculated EKR_ct/V values. It is apparent that all of these calculations of dose agree closely, and that the mean values for corrKt/VDaug and EKR_ct/V are almost identical per session and per week. These clinical data demonstrate that the EKR parameter is almost identical to TAK, and it can be concluded that EKR does not account for the first order nature of dialysis therapy, and is therefore not suitable to normalize dose for varying treatment schedules.

Fig. 1 graphically illustrates this conclusion. The weekly values for corrKt/VDaug and EKR_ct/V are both plotted as a function of eKt/V per session. These two weekly dose parameters for daily dialysis can be seen to be identical summations of the individual Kt/V values, as shown in Table I. Note that the weekly EKR_ct/V plotted for thrice-weekly dialysis indicates that a weekly Kt/V of 3.2 would be required for CAPD therapy clinically equivalent to that in twHD with an eKt/V of 1.05.

In contrast, the curves for stdKt/V in Fig. 1, plotted for 3- and 6-times-weekly dialysis as a function of individual eKt/V values, are highly curvilinear. They reflect decreasing efficiency with increasing eKt/V per session. Notice that, on the curve for N = 3, identical stdKt/V values of 2.0 are predicted for adequate CAPD and twHD. As noted above, the EKR_ct/V line for N = 3 predicts that CAPD would require a weekly Kt/V of 3.2 for therapy equivalent to an eKt/V of 1.05 in twHD, and that a weekly Kt/V of 2.0 in CAPD would be grossly inadequate therapy corresponding to an eKt/V of 0.68 in twHD. These relationships for EKR_c are highly inconsistent with clinical experience and results, because the

TABLE I Comparison of Kt/V (Daugirdas) to $EKR_c t/V$.

Patient	*t (Min)*	*Kt/V per session (Daugirdas)*	*Corrected Kt/V per session (Daugirdas)*	*$EKR_c t/V$ per session*	*Corrected Kt/V weekly (Daugirdas)*	*$EKR_c t/V$ weekly*
1	135	0.73	0.67	0.71	4.02	4.26
2	150	0.89	0.84	0.83	5.04	4.98
3	158	0.65	0.60	0.63	3.60	3.78
4	120	0.72	0.65	0.68	3.90	4.08
5	120	0.74	0.67	0.70	4.02	4.20
6	135	0.81	0.75	0.77	4.50	4.62
7	165	0.79	0.74	0.74	4.44	4.44
8	128	0.97	0.92	0.87	5.52	5.22
9	150	0.86	0.81	0.80	4.86	4.80
10	135	0.94	0.89	0.87	5.34	5.22
11	121	0.63	0.57	0.61	3.42	3.66
12	158	0.87	0.83	0.80	4.98	4.80
13	120	0.83	0.76	0.78	4.56	4.68
Mean±SD		0.80±0.10	0.75±0.11	0.75±0.08	4.48±0.66	4.52±0.50

$EKR_c t/V$ = corrected equivalent renal clearance.

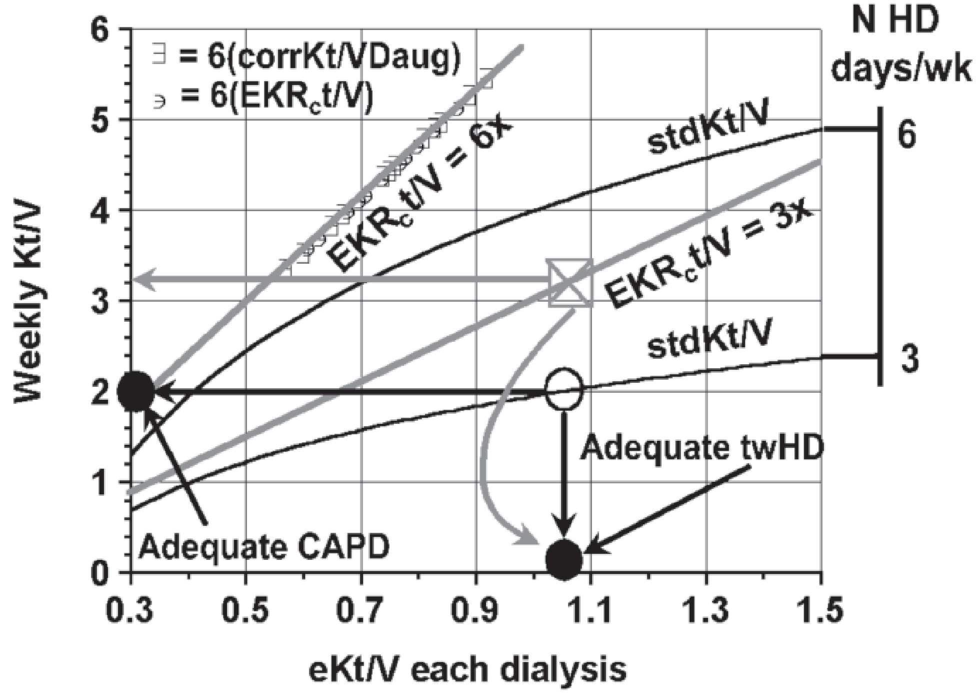

FIGURE 1 Weekly corrected equivalent renal clearance ($EKR_c t/V$) and corrected Kt/V from the Daugirdas formula (corrKt/VDaug) are calculated from the data of Piccoli *et al.* [1] and plotted as a function of session equilibrated Kt/V (eKt/V). Note that both parameters agree well with a linear function (y = 6x). Solution of the standard Kt/V (stdKt/V) model for N = 3 and N = 6 is also shown, as is the relation expected for $EKR_c t/V$ with N = 3. Only the stdKt/V for N = 3 correctly predicts the dose of adequate continuous ambulatory peritoneal dialysis (CAPD) and thrice-weekly hemodialysis (twHD).

model fails to account for the first order nature of dialysis therapy.

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