Modeling the Dose of Home Dialysis

Frank A. Gotch

San Francisco, California, U.S.A.

*T*he growing interest in daily dialysis and combined continuous and intermittent dialysis treatments has created the need for a dialysis dosing model that is valid over a wide range of dosing frequency and intensity. Three models have been described for this purpose and are reviewed here. They have in common the concept of a continuous clearance value which is equivalent to the summed intermittent dialysis prescribed. The continuous clearance models all define a point on the saw-toothed blood urea nitrogen (BUN) concentration profile and calculate the continuous clearance required to achieve this at the same urea generation rate. The points modeled are the peak predialysis concentration (pkKt/V), the average Co (standard Kt/V, stdKt/V), and time-averaged urea concentration (TAC), which is termed equivalent renal clearance (EKRt/V). At the present time the only data for evaluation of clinical relevance of the three models is continuous ambulatory peritoneal dialysis (CAPD) outcome. The stdKt/V predicts that optimal CAPD outcome requires weekly stdKt/V 2.0, while the pkKt/V and EKRt/V models predict optimal doses of 1.8 and 3.0. These results suggest that the stdKt/V is the most realistic model, but data over much higher levels of therapy are not yet available to judge generalizability. The stdKt/V model was used to assess dose in two hemodialysis studies with 5 to 6 dialyses per week and showed that in one study the stdKt/V was only 2.0, while in the second study it was 5.6. These results show that dose can vary widely with a similar number of dialyses per week and point to the need for a generalized dosing model to guide and compare studies of daily home dialysis.

Key words

Introduction

There is growing interest in more frequent hemodialysis (4 to 7 times/week), which, in turn, is driving renewed interest in home hemodialysis, since it is financially much more feasible to increase dialysis frequency in the home setting. Underlying the interest in increased dialysis frequency is the hypothesis

Correspondence to:

Frank A. Gotch, MD, 144 Belgrave Ave., San Francisco, California 94117 U.S.A.

email: frank.gotch@fmc-na.com

that outcomes will improve as we approach a continuous form of dialysis therapy.

The classical concept of single pool Kt/V (spKt/V) to quantify dialysis dose is based on a fixed thrice-weekly treatment schedule [1]. More recently, the equilibrated Kt/V (eKt/V) has been advanced as a better kinetic description of the dose [2,3]. Large database analysis has indicated that an eKt/V of 1.0 – 1.1 represents an adequate thrice-weekly hemodialysis prescription [4], and the prospectively randomized HEMO study [5] now under way will compare outcomes with eKt/V 1.05 to those with eKt/V 1.45.

Theoretical models of equivalent continuous clearance

It must be emphasized that the above criteria for eKt/V refer only to a thrice-weekly dialysis treatment schedule. More generalized descriptions of dosage encompassing different schedules of dialysis frequency have recently been reported [6–10]. All of these models have in common the definition of a theoretical continuous urea clearance which is considered to be *therapeutically equivalent* to the sum of intermittent clearances provided by intermittent dialysis therapy. The models differ only in how the target blood urea nitrogen (BUN) relative to the urea generation rate (Gu) is defined.

In all models of theoretical equivalent continuous clearance a modeling point is chosen on the saw-toothed BUN profile characteristic of intermittent dialysis therapy, and the continuous clearance necessary to maintain BUN at this level is calculated. This is illustrated graphically in Fig. 1, where the BUN profile characteristic of a thrice-weekly dialysis schedule is plotted. The modeling loci that have been reported are the peak concentration [6], the mean concentration [7,8], and the time-averaged concentration [9,10].
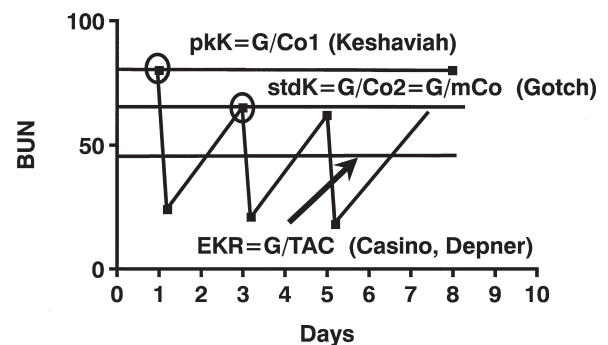

FIGURE 1   Three theoretical definitions of continuous urea clearance proposed for modeling equivalent therapy in hemodialysis and continuous ambulatory peritoneal dialysis.

In the steady state (ss), the relationship between urea generation rate (Gu), ss clearance (Kss), and concentration (Css) is

$$Gu = Kss(Css). \qquad (1)$$

Note: Equation (1) states that in steady state there is no accumulation of urea, since the removal rate, Kss(Css), is equal to the generation rate, Gu. If the expression is rearranged, we can show

$$Kss = Gu/Css. \qquad (2)$$

The three models of theoretical therapeutically equivalent continuous clearance differ only with respect to the concentration term, Css. Unlike continuous ambulatory peritoneal dialysis (CAPD), where clearance is virtually continuous and BUN constant, there is no steady-state concentration in intermittent dialysis therapy as can be seen in Fig. 1. However, we can define theoretical therapeutically equivalent steady states as follows. If we assume that continuous therapy, which achieves Css equal to the maximum or peak predialysis concentration (pkCo or Co1) of intermittent therapy, is therapeutically equivalent to intermittent therapy, we can define this equivalent continuous clearance (pkK) as

$$pkK = Gu/Co1 = Gu/pkCo = Gu/Cpkss = Kpkss. \qquad (3)$$

This has been described as the peak concentration hypothesis [6] and uses the preconcentration for the first dialysis of the week on a thrice-weekly schedule to model the pkK.

A second definition of theoretical continuous clearance is based on the average or mean predialysis concentration, mCo, using the second or midweek dialysis, Co2, on a thrice-weekly schedule and expressed as a standard clearance [8] or stdK,

$$stdK = Gu/Co2 = Cu/mCo = Gu/Comss = Kmss. \qquad (4)$$

This model has been generalized for application to any treatment frequency and schedule by solution for mCo and Gu [8]. A third definition is based on the time-averaged urea concentration (TAC) throughout the week [9,10] and has been called the "equivalent renal clearance," or EKR, by the authors. The mathematical expression is

$$EKR = Gu/TAC = Gu/Ctacss = Ktacss. \qquad (5)$$

The EKR model has also been generalized. Note that Eqs. (3) to (5) differ only in how concentration is defined, and the terms pkCo, mCo, and TAC are all theoretical surrogates considered to be *therapeutic steady-state concentration equivalents* of Css in Eq. (2).

How can we evaluate the validity of these three models? At the present time, the only data available to evaluate the clinical relevance of the three theoretical definitions of equivalent continuous clearance, pkK, stdK, and EKR are clinical outcomes in CAPD compared to thrice-weekly hemodialysis. The magnitude of therapy provided in CAPD expressed as a weekly Kt/V is the weekly continuous peritoneal urea clearance, where K is considered to be Kss, normalized to volume. The weekly urea concentration profile can be readily computed for intermittent thrice-weekly hemodialysis therapy [7,8]. The three theoretical continuous clearances can be computed from pkCo, mCo, and TAC and the results expressed as the weekly pkKt/V, stdKt/V, or EKRt/V. Such a set of calculations is shown in Fig. 2, where the abscissa represents levels of eKt/V in thrice-weekly hemodialysis (HD), and the ordinate represents weekly equivalent Kt/V (eqKt/V) calculated for pkKt/V, stdKt/V, or EKRt/V. Currently, an eKt/V of 1.05 is considered adequate HD, while the current HEMO study [5] prospectively compares clinical outcome with 1.05 to a much larger dose, eKt/V 1.45. The three theoretical continuous clearance values were computed as a function of eKt/V and are plotted in Fig. 2. Fixed-volume single pool kinetics [8] were used to compute single pool Kt/V (spKt/V), and these values converted to eKt/V using the Tattersall rate equation [3]. The effects of variable treatment time for intermittent HD are accounted for in the model by expressing the results as eKt/V, although ultra-filtration requirements would impose variable constraints on the time parameter for individual patients.

Note the stdKt/V curve predicts that a weekly stdKt/V of 2.0 is equivalent to HD eKt/V of 1.05 and agrees well with current dosage recommendations in CAPD and HD. The pkKt/V curve indicates that a weekly pkKt/V of 1.75 is equivalent to eKt/V 1.05, which is now considered inadequate for CAPD therapy. The EKRt/V curve indicates that a weekly EKRt/V of 3.0 would be required for CAPD therapy equivalent to thrice-weekly HD with eKt/V 1.05. The EKRt/V

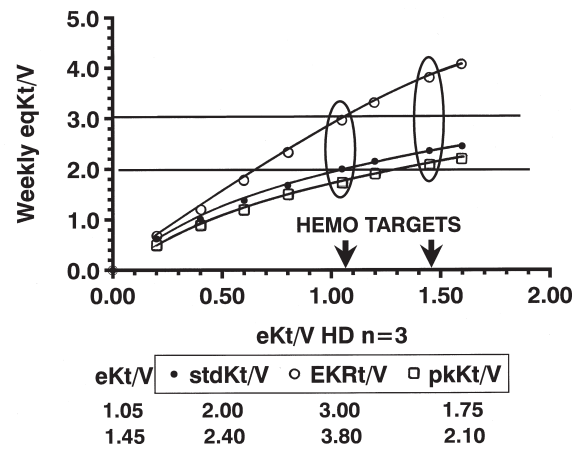| eKt/V	• stdKt/V	○ EKRt/V	□ pkKt/V
1.05	2.00	3.00	1.75
1.45	2.40	3.80	2.10

FIGURE 2 Clearance targets for continuous ambulatory peritoneal dialysis relative to hemodialysis, calculated from the three theoretical definitions of equivalent continuous clearance: stdKt/V, EKRt/V, and pkKt/V.

relationship to eKt/V implies that with current CAPD therapy and weekly Kt/V of 2.0, the relative risk of mortality in CAPD should be 50% higher than in HD, since an eqKt/V of 2.0 can be seen to correspond to eKt/V of 0.6 in Fig. 2. The relationships in Fig. 2 provide support for the therapeutic validity of the stdKt/V parameter but do not support therapeutic validity of the pkKt/V and EKRt/V models.

Generalized solution of the stdKt/V model

As noted above, the stdKt/V model can be solved for any specified frequency of dialysis or combination of intermittent dialysis and daily continuous renal function or CAPD [8]. Such a generalized model solution is depicted in Fig. 3, where a family of weekly stdKt/V curves is plotted as a function of the number of days per week (*N*) the patient is hemodialyzed, ranging from 2 to 7, and the level of eKt/V delivered during each dialysis, ranging from 0 to 1.5 over 4 hours. Again, it can be noted that a weekly stdKt/V of 2.0 corresponds to eKt/V of 1.05 three times weekly. All the curves are logarithmic and approach individual limiting values as a function of *N* as eKt/V increases, because intradialytic BUN falls to very low levels at high eKt/V, and dialysis becomes less and less efficient with respect to solute removal. The straight line labeled Continuous Clearance in Fig. 3 simply has a slope of 7 and is defined such that each eKt/V on the abscissa is considered to be delivered daily and continuously, and the line is therefore an expression of weekly stdKt/V. This line represents the maximal values that stdKt/V can reach with continuous therapy.

Levels of stdKt/V calculated for two classic studies of home HD

It is instructive to use the stdKt/V model to quantitatively assess the dialysis doses in two classic studies of home HD [11,12]. In 1972 Bonomini and colleagues reported marked clinical improvement associated with changing from 2 dialyses/week (32 patients) to 3 dialyses/week (7 patients) to 5 dialyses/week (6 patients). The most dramatic change was from 2 to 3 with a much smaller increment in improvement with 5 dialyses/week. This paper was recently reprinted in *Seminal Contribution to Dialysis* with an accompanying editorial suggesting Kt/V no longer has validity as a dosing model in view of clinical outcome with more frequent dialyses and calls for new, but unspecified, models to describe dialysis treatment [13].

The level of therapy in Bonomini's patients can be reasonably well estimated from the pre- and post-BUN plots with twice-weekly and daily HD reported in the paper. These plots were used to estimate spKt/V using the Daugirdas algorithm [14] and then to calculate eKt/V [2,3]. The results indicate that the eKt/V with twice- and thrice-weekly dialysis was 0.88, and for 5 times weekly dialysis it was 0.50. The weekly stdKt/V levels were calculated for each of these therapies with results shown in Fig. 4. It can be seen that the stdKt/V levels were 1.2, 1.8, and 2.0 with 2, 3, and 5 dialyses per week, respectively. This study sheds little light on the merits of daily dialysis. When the doses are examined quantitatively, it appears that the study compared what we now know to be grossly inadequate twice-weekly dialysis (stdKt/V 1.2) and marginally adequate thrice-weekly dialysis (stdKt/V 1.8) to the level of therapy (stdKt/V 2.0), which is equivalent to eKt/V 1.05 with thrice-weekly dialysis, comparable to the low dose target in the HEMO study.

In 1988 Pierratos and colleagues [12] reported their experience with long overnight HD with average treatment time of 8.9 hours and an average of 5.6 treatments per week. Average pre- and post-BUN profiles for thrice- and 5.6 times weekly therapy were shown, and from these curves spKt/V and eKt/V values were calculated with results also plotted in Fig. 4. The level of therapy on thrice-weekly dialysis in these patients was very high with mean eKt/V 1.37 and therefore
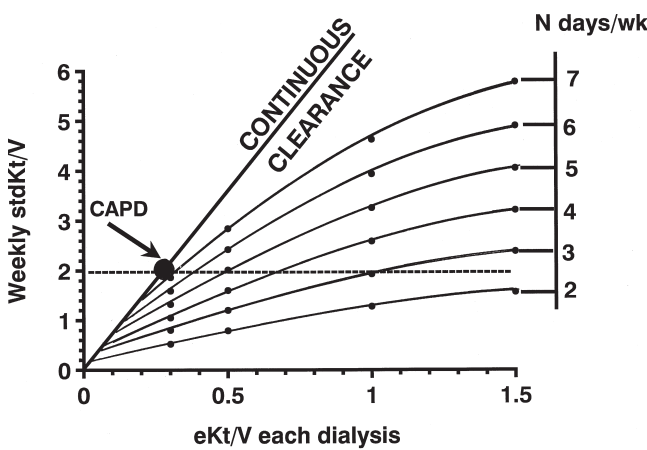

FIGURE 3   The interrelationships between eKt/V delivered each dialysis, number of days dialyzed per week, and the level of weekly stdKt/V achieved.
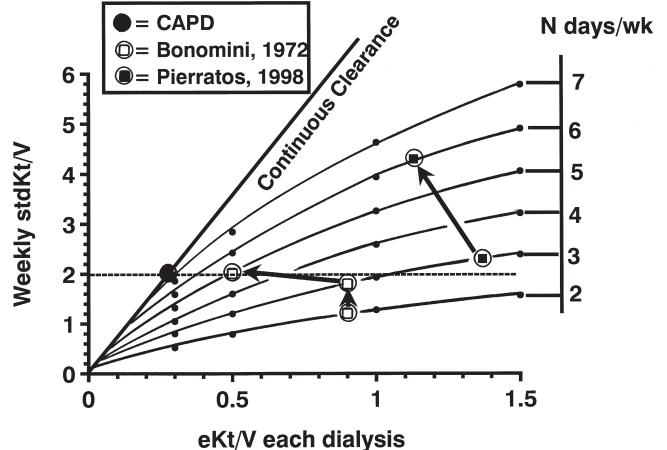

FIGURE 4   The loci of stdKt/V calculated for two widely quoted studies of home hemodialysis with 5.0 – 5.6 dialyses per week.

stdKt/V 2.3. The eKt/V achieved with 5.6 dialyses per week was 1.13, which resulted in stdKt/V 4.3 as depicted in Fig. 4. Note that the dialysis dose on thrice-weekly therapy calculated from the Pierratos data was nearly as high as that calculated from Bonomini data for 5 treatments per week. The Pierratos dose with 5.6 treatments per week was much higher (172%) than the dose provided by Bonomini with 5 treatments per week (stdKt/V 4.3 and 2.0, respectively).

Discussion

Design and analysis of new forms of dialysis therapy with variably increased intensity and frequency of dialysis require a quantitative dosing model that is valid over a wide range of dose intensity and frequency. The stdKt/V urea model provides a method to express the dose normalized to volume as a theoretical continuous clearance therapeutically equal to any schedule and intensity of intermittent clearance. Clinical assessment of CAPD outcome relative to thrice-weekly HD provides support for the model's therapeutic validity, but studies with more frequent dialysis of variable intensity (i.e., stdKt/V) and rate (i.e., treatment time, or t) are required to determine the clinical generalizability of the model. In this context it should be emphasized that only one clinical outcome point on the stdKt/V curves (CAPD vs thrice-weekly HD with eKt/V 1.05) has been verified to date. All relationships of outcome to dialysis dosing established to date are empirically based, and the mechanisms underlying the relationships (such as control of fluid balance and variable solute distribution kinetics) remain to be established. However, analysis of two classical studies of home dialysis with the stdKt/V model provided a valuable perspective on magnitude of therapy provided in the two studies.

References

1 Gotch F. Sargent J. A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). Kidney Int. 28: 526–34. 1985.

2 HEMO Study Group. (Prepared by Daugirdas J. Depner T. Gotch F. Greene T. Keshaviah P. Levin N. Schulman G.) Comparison of methods to predict equilibrated Kt/V in the Hemodialysis (HEMO) Pilot Study. Kidney Int. 52: 1395–405. 1997.

3 Tattersall J. DeTakats D. Chamney P. Greenwood R. Farrington K. The post-hemodialysis rebound: predicting and quantifying its effect on Kt/V. Kidney Int. 50: 2094–102. 1996.

4 Gotch F. Levin N. Port F. Wolfe R. Uehlinger D. Clinical outcome relative to the dose of dialysis is not what you think: the fallacy of the mean. Am J Kidney Dis. 30: 1–15. 1997.

5 Eknoyan G. Levey A. Beck G. Agodoa L. Daugirdas J. Kusek J. Levin N. Schulman G. For the HEMO Study Group. The Hemodialysis (HEMO) Study: rationale for selection of interventions. Semin Dial. 9: 24–33. 1996.

6 Keshaviah P. Nolph K. Van Stone J. The peak concentration hypothesis: a urea kinetic approach to comparing adequacy of continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis. Perit Dial Int. 9: 69–72. 1989.

7 Gotch F. Keen M. Kinetic modeling in peritoneal dialysis. In: Clinical dialysis. 3rd ed. Nissenson A. Fine R. Gentile D. eds. Appleton & Lange. 1995: 343–76.

8 Gotch F. The current place of urea kinetic modelling with respect to different dialysis modalities. Nephrol Dial Transplant. 13(Suppl 6): 10–14. 1998.

9 Casino F. Lopez F. The equivalent renal ura clearance: a new parameter to assess dialysis dose. Nephrol Dial Transplant. 11: 1574–81. 1996.

10 Depner T. Benefits of more frequent dialysis: lower TAC at the same Kt/V. Nephrol Dial Transplant. 13(Suppl 6): 20–4. 1998.

11 Bonomini V. Mioli A. Albertazzi. Scolari P. Daily-dialysis programme: indications and results. Nephrol Dial Transplant. 13: 2774–8. 1998.

12 Pierratos A. Ouwendyk M. Francoeur R. Vas S. Raj D. Eddlestone A. Langos V. Udall R. Nocturnal hemodialysis: three year experience. J Am Soc Nephrol. 9: 859–68. 1998.

13 Bommer J. Vos P. Kooistra M. Ritz E. Comment. Nephrol Dial Transplant. 13: 2777–8. 1998.

14 Daugirdas J. Second generation logarithmic estimation of single pool-variable volume Kt/V: an analysis of error. J Am Soc Nephrol. 4: 1205–13. 1993.