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Relationship between apparent (single-pool) and true (double-pool) urea distribution volume

John T. Daugirdas, Tom Greene, Thomas A. Depner, Frank A. Gotch, Robert A. Star, and the Hemodialysis (HEMO) Study Group

NIDDK, National Institutes of Health, Bethesda, Maryland, USA

Relationship between apparent (single-pool) and true (double-pool) urea distribution volume.

Background. The volume of urea distribution (V) is usually derived from single-pool variable volume urea kinetics. A theoretical analysis has shown that modeled single-pool V (Vsp) is overestimated when the urea reduction ratio (URR) is greater than 65 to 70% and is underestimated when the URR is less than 65%. The "true" volume derived from double-pool kinetics (Vdp) does not exhibit this effect. An equation has been derived to adjust Vsp to the expected Vdp.

Methods. To validate these theoretical predictions, we examined data from the Hemodialysis (HEMO) Study to assess the performance of Vdp as estimated from Vsp using the previously published prediction equation. For increased precision, both Vsp and Vdp were factored by anthropometric volume (Va). Patients were first dialyzed with a target equilibrated dialysis dose (eKt/V) of 1.45 during a baseline period and were then randomly assigned to eKt/V targets of either 1.05 (a URR of approximately 67%) or 1.45 (a URR of approximately 75%). A blood sample was obtained one hour after starting dialysis during one dialysis in each patient.

Results. Vsp/Va was (mean ± SD) 1.014 ± 0.127 in 795 patients during the baseline period when the URR was approximately 1.45. During the first modeled dialysis after randomization, the Vsp/Va fell to 0.961 ± 0.138 in the group with an eKt/V target of 1.05, but did not change significantly under the high eKt/V goal. The correction of Vsp to Vdp using the prediction equation resulted in a Vdp/Va ratio of 0.96 to 0.98 in all three circumstances without significant differences. When a blood sample was drawn one hour after starting dialysis, the apparent Vsp/Va ratio at one hour was much lower at 0.708 ± 0.139. However, the mean Vdp/Va ratio, computed using the correction equation, was 0.968 ± 0.322, which was similar to the Vdp/Va ratio calculated from the postdialysis blood urea nitrogen.

Conclusions. These data suggest that the previously derived formula for adjusted Vsp is valid experimentally. The Vsp/Vdp correction should be useful for prescribing hemodialysis with either a very low Kt/V (for example, daily and early incremental dialysis) or a very high Kt/V.

Key words: dialysis, urea kinetic modeling, volume of urea distribution, anthropometric volume.

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One of the advantages of measuring Kt/V during hemodialysis instead of a simple determination of the urea reduction ratio (URR) is the ability to calculate the patient's urea distribution volume (V) from measured or estimated values of treatment time (t) and the dialyzer clearance (Kd). The value thus obtained for V can be compared with the patient's true V obtained from a variety of sources, including the mean of previous Kt/V estimates of V or from anthropometrically derived or bioimpedance measurements of total body water (TBW). Significant differences suggest that one or more input measures [pre-blood urea nitrogen (BUN) or post-BUN values, estimated dialyzer clearance, or session length] are erroneous. Sequential monitoring of the hemodialysis-derived value for V allows one to detect changes in dialysis efficiency; for example, an increase in V results from an unprescribed decrease in effective dialyzer clearance. The latter may be caused by access recirculation, a decrease in blood flow rate caused by prepump pressure effects on the blood line pump segment, or errors in the reprocessing procedure. When the prescription is changed to a higher or lower value of Kt/V or URR, V is assumed to remain constant. However, if Kt/V is determined from variable volume single-pool modeling of the predialysis and postdialysis BUN, V (Vsp) has been shown to vary slightly when calculated as described above from t and Kd [1–4]. This could lead to errors in prescribed blood flow, dialysate flow, or time on dialysis when the prescription is changed to achieve a new level of adequacy based on single-pool urea kinetics.

The simple single-pool model assumes that urea is removed from a single space during dialysis. As dialysis efficiency levels have increased over that past two decades, urea compartmentalization during hemodialysis has assumed a more prominent role. Compartmentalization causes a rapid initial decrease in the blood urea

concentration [5] and a similar rapid postdialysis increase in blood urea concentration as sequestered urea equilibrates with the dialyzed compartment [1, 2]. These effects can alter the relationship between V and Kd when their ratio (Kd/V) is determined from a mathematical model that ignores disequilibrium [1–4]. A recent analysis of simplified double-pool equations, assuming no ultrafiltration and no urea generation during hemodialysis, resulted in a mathematical correction factor for Vsp that quantifies the relationship between the "single-pool" V (Vsp) and true V determined by double-pool modeling (Vdp) [4]. The ratio Vsp/Vdp was found to be a function of the URR and a factor, Fdp, that is the ratio of the end dialysis to equilibrated postdialysis urea nitrogen concentration. Fdp is related to dialysis efficiency and was found to be approximately 0.82 when dialysis was delivered at 0.4 single-pool Kt/V units/hr. Regardless of dialysis efficiency and the value for Fdp, the Vsp/Vdp ratio was found to approach unity at a URR of approximately 0.67, corresponding to a single-pool Kt/V value of approximately 1.3. When Kt/V is lower than this value, the analysis predicts that Vsp will be lower than Vdp. When Kt/V is greater than 1.3, the analysis predicts that Vsp/Vdp will be greater than unity.

Because the mean spKt/V delivered in the United States in 1996 is close to 1.3 [6], which is the level at which Vsp is equal to Vdp, discrepancies between Vsp and Vdp will often be of little clinical importance. However, as shown previously [4], the error in Vsp requires a greater than expected increase in dialysis time when the dose of dialysis is increased. Also, with increasing interest in daily hemodialysis and lower Kt/V values per treatment, it can be expected that levels of Vsp/Vdp substantially less than unity will be encountered and that substantial errors in the prescription can be anticipated unless a correction is applied.

The analytically derived relationships between Vsp and Vdp have not previously been tested using patient data. The National Institutes of Health (NIH) Hemodialysis (HEMO) Study has provided initial data in patients who were randomly assigned to a prescribed eKt/V of 1.05 or 1.45. In addition, during certain dialysis sessions, a blood sample was obtained one hour after starting dialysis when eKt/V was approximately 0.50. These data provided an opportunity to evaluate the analytically derived relationship between Vsp and Vdp, and whether the computation of Vdp would help to prescribe hemodialysis more accurately.

METHODS

In the design of the HEMO Study, patients were first evaluated during a baseline period when their ability to attain the high goal therapy (equilibrated Kt/V = 1.45) was tested. To qualify for randomization, the eKt/V needed to be greater than 1.30 during at least two of three successive modeled dialyses targeted at the eKt/V goal of 1.45. After randomization, half of the patients were continued on the high-goal prescription, and in the remainder, the prescription was targeted at the standard eKt/V goal of 1.05. Once randomized, patients had monthly predialysis and postdialysis blood samplings for BUN that were used to compute single-pool Kt/V (spKt/V) and equilibrated Kt/V (eKt/V). At month 4 (F4), additional blood samples were drawn at one hour (inlet × 2 and outlet). The predialysis specimen was drawn from the dialyzer inlet (arterial) bloodline before giving saline or heparin. The one-hour and postdialysis samples were drawn 15 to 20 seconds after slowing the blood pump to 50 to 80 ml/min.

For this article, the first 795 randomized patients were analyzed only if the initial post-randomization session was taken within 30 days of randomization (to minimize the chance of any physiologically mediated change in TBW and V), and an F4 modeling session was done. Twenty-three F4 modeled dialyses—and therefore patients—were excluded based on an outliers rule, which held that if the one-hour BUN was less than 80% of the predialysis value or if the postdialysis BUN (20-second slow flow sample) was more than 90% of the one-hour BUN value, the BUN sampling or laboratory analysis was most probably in error.

Single-pool kinetic equations

The 2-BUN variable volume single-pool model described by Depner and Cheer was used [7]. Dialyzer clearance was estimated from the mass transfer area coefficient (KoA), blood flow rate, and dialysate flow rate. The KoA values used were determined based on *in vitro* results with the study dialyzers, as reported previously [8]. Nominal blood flow rates were adjusted as reported previously to account for incomplete filling of the pump segment of the dialyzer bloodline at lower prepump pressures [9]. The algorithm was based solely on the nominal blood flow rate. For every 100 ml/min nominal flow greater than 200 ml/min, the nominal dialyzer blood flow rate (Qb) was reduced by 5%: for example, by 5% for Qb = 300 and by 10% for Qb = 400. The urea clearance correction for blood water was 10%.

Computation of single pool urea volume

Unadjusted Vsp. The iterative 2-BUN method adjusts the urea generation rate G until the estimated predialysis BUN at a weekly steady state is nearly identical to the actual predialysis BUN [7]. After each iteration, Vsp is recalculated from standard variable-volume, single-pool equations, based on the estimated Kd, G, ultrafiltration rate, dialysis time, and predialysis and postdialysis BUN values.

Vsp at one hour. Vsp cannot be estimated by directly

applying the 2-BUN method to the BUNs obtained predialysis and at one hour because the 2-BUN method assumes that dialysis ends at the time of the second blood draw for determination of G. To avoid this difficulty, we first estimated G by applying the 2-BUN method to the predialysis and postdialysis BUNs [7]. Thus, using this value of G as an input parameter, we used the standard variable-volume, single-pool equations to calculate V from the predialysis and one-hour BUNs.

Adjusted Vsp. As described previously, the adjusted Vsp, which estimates the theoretical double-pool volume Vdp, is computed from a ratio of Vsp/Vdp [4]:

$$\text{Vsp/Vdp} = \ln[(\text{Fdp} \times \text{BUNpre/BUNpost})]/[\text{Fdp} \times \ln(\text{BUNpre/BUNpost})] \quad \text{(Eq. 1)}$$

where Fdp = BUNpost/BUNeq. The application of Equation 1 requires an estimate of the equilibrated postdialysis BUN (BUNeq). In the HEMO Study, equilibrated Kt/V (eKt/V) is estimated using the rate equation for arteriovenous accesses [10–13]:

$$\text{eKt/V} = \text{spKt/V} - 0.6(\text{spKt/V})/\text{Td} + 0.03 \quad \text{(Eq. 2)}$$

where Td is the dialysis time in hours. Because "K" in the expression "eKt/V" is the patient's whole body clearance (Kwb):

$$\text{Kwb/Vdp} = (\text{eKt/V})/\text{Td} \quad \text{(Eq. 3)}$$

Finally, given Kwb/Vdp, the 2-BUN algorithm can be modified to determine BUNeq and the equilibrated urea generation rate (eG) [13]. In this application of the 2-BUN algorithm, Kwb/Vdp is used as an input parameter in place of the parameter Kd/Vsp to solve for the equilibrated postdialysis BUN (BUNeq) and urea generation rate (eG). Let *m* denote the function that determines BUNeq and eG from Kwb and Vdp by this method so that:

$$(\text{BUNeq, eG}) = \text{m(Kwb, Vdp)} \quad \text{(Eq. 4)}$$

Equation 4 actually gives two independent relationships to define both BUNeq and eG, so that Equations 1, 3, and 4 combine to define four independent relationships to determine uniquely the four parameters Kwb, Vdp, BUNeq, and eG. The values of these four parameters, including BUNeq, were calculated by iterative application of Equations 1, 3, and 4 using Vsp as an initial estimate for Vdp. Convergence of all parameters to within 0.01% was achieved within five iterations for all modeled dialyses.

Because of the complexity of this algorithm, we considered a simpler direct approximation for the value of BUNeq to be substituted in Equation 1. In this approximation, Equation 2 is again used to determine eKt/V. Given estimates for both spKt/V and eKt/V, BUNeq was estimated as follows:

First compute the coefficient *a* where:

$$\text{spKt/V} = \text{a} \times \ln(\text{BUNpre/BUNpost})$$

then use *a* to solve for BUNeq in the equation:

$$\text{eKt/V} = \text{a} \times \ln(\text{BUNpre/BUNeq})$$

Thus,

$$\text{BUNeq} = \text{BUNpre}^{1-r} \times \text{BUNpost}^{r}$$

where

$$r = (\text{eKt/V})/(\text{spKt/V}) \quad \text{(Eq. 5)}$$

From BUNeq, we determined Fdp = BUNpost/BUNeq, and subsequently, Vsp/Vdp by Equation 1, and then Vdp = Vsp/(Vsp/Vdp).

The values of BUNeq computed using Equation 5 were very similar to the values of BUNeq based on the more complex iterative method based on Equations 1, 3, and 4. At the first follow-up session, the Pearson correlation between these methods was more than 0.999. The concordance correlation was 0.999, and the median absolute deviation was 0.25 mg/dl. A similar level of agreement was obtained at other time points. Because of this high level of agreement, we shall consider only the direct approximation during the remainder of the article.

Computation of anthropometric volume

Anthropometric volume (Va) was calculated using the equations proposed by Watson, Watson, and Batt based on the postdialysis weight, height, gender, and age [14].

Statistics

Comparisons of unadjusted Vsp and the estimated Vdp are based on the volume ratios Vsp/Va and Vdp/Va in order to control for variability in patient size. Comparisons are regarded as statistically significant if $P < 0.05$, two-sided. All results are summarized as mean ± SD unless specified otherwise.

RESULTS

At baseline during the high target test period

Vsp/Va ratios. These results are presented in Table 1 and the left panel of Figure 1. The Vsp/Va ratios were 1.016 ± 0.132 and 1.011 ± 0.122 in the groups destined to be randomized to the standard and high treatment arms, respectively (P = NS).

Vdp/Va ratios (using approximate algorithm for Vdp). During this same period, the Vdp/Va ratios were substantially and significantly lower than the Vsp/Va ratios ($P < 0.001$). The Vdp/Va ratios were 0.968 ± 0.136 for those destined for the standard treatment group and

Table 1. Kinetic parameters and Vsp/Vdp adjustment in baseline and first follow-up

	Randomized to high goal (eKt/V = 1.45	Randomized to standard goal (eKt/V = 1.05)
Baseline period during testing of high goal		
URR	0.759 ± 0.027	0.755 ± 0.028
spKt/V	1.72 ± 0.14	1.70 ± 0.14
eKt/V	1.47 ± 0.12	1.45 ± 0.11
Qb *ml/min*	414 ± 51	414 ± 49
Qd *ml/min*	701 ± 120	698 ± 118
KoA *ml/min*	929 ± 162	943 ± 167
Kd *ml/min*	272 ± 26	273 ± 26
Session length *min*	219 ± 24	220 ± 26
Unadjusted Vsp *liter*	35.0 ± 6.3	35.9 ± 7.1
K/V hr^{-1}	0.48 ± 0.07	0.47 ± 0.08
Fdp value	0.808 ± 0.029	0.811 ± 0.033
Vsp/Va	1.011 ± 0.122	1.016 ± 0.132
Vdp/Va	0.961 ± 0.123	0.968 ± 0.136
First follow-up session after randomization		
URR	0.751 ± 0.040	0.669 ± 0.048
spKt/V	1.68 ± 0.19	1.34 ± 0.17
eKt/V	1.43 ± 0.16	1.11 ± 0.15
Qb *ml/min*	415 ± 53	352 ± 75
Qd *ml/min*	712 ± 117	636 ± 134
KoA *ml/min*	925 ± 150	861 ± 157
Kd *ml/min*	272 ± 24	240 ± 31
Session length *min*	215 ± 26	188 ± 26
Vsp (unadjusted)	35.5 ± 7.3	34.1 ± 7.6
K/V hr^{-1}	0.48 ± 0.08	0.44 ± 0.08
Fdp value	0.808 ± 0.035	0.825 ± 0.034
Vsp/Va	1.026 ± 0.164	0.961 ± 0.138
Vdp/Va	0.979 ± 0.175	0.959 ± 0.148

Data are mean ± SD. Abbreviations are: URR, urea reduction ratio; spKt/V, single-pool dialysis dose; eKt/V, equilibrated dialysis dose; Qb, dialyzer blood flow rate; Qd, blood flow rate; KoA, mass transfer area coefficient; Kd, dialyzer clearance; Vsp, volume derived from single pool kinetics; K/V, clearance per volume; Fdp, blood urea nitrogen (BUN) post/BUNeq; Vsp/Va, single pool kinetics volume/anthropometric volume; Vdp/Va, double pool kinetics volume/anthropometric volume.

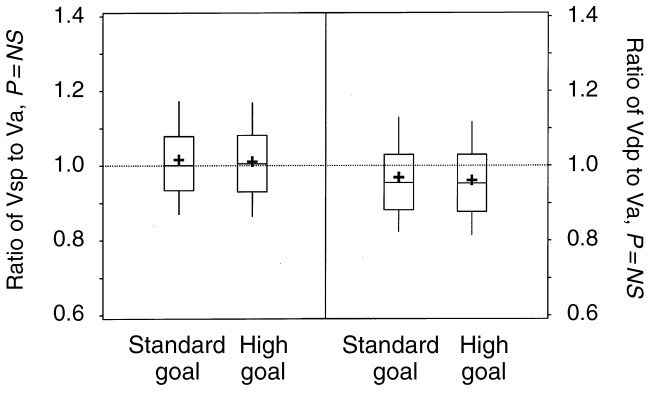

Fig. 1. (Left panel) Vsp/Va ratios at baseline for patients destined for the standard and high Kt/V goals. (Right panel) Vdp/Va ratios at baseline for patients destined for the standard and high Kt/V goals. At baseline, for testing purposes, both standard and high goal groups were studied at high goal URR and Kt/V values.

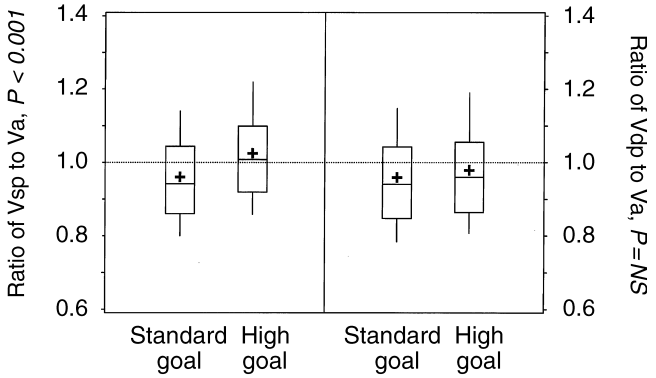

Fig. 2. (Left panel) One-month follow-up Vsp/Va ratios in standard and high Kt/V goals. (Right panel) One-month follow-up Vdp/Va ratios in standard and high Kt/V goals.

0.961 ± 0.123 for those to be randomized to the high-treatment arm. A comparison of Vdp/Va ratios between the two groups showed no significant difference (Fig. 1, right panel).

During the first modeling session after randomization

eKt/V values. The mean delivered eKt/V was 1.11 ± 0.15 in the standard treatment arm and 1.43 ± 0.16 in the high treatment arm.

Vsp/Va values. Whereas the Vsp/Va ratios in the two groups had been similar at baseline, there was now a marked difference ($P < 0.001$) between the two groups (Fig. 2, left panel). In the standard arm, the Vsp/Va ratio was 0.961 ± 0.138, whereas in the high goal arm Vsp/Va was 1.026 ± 0.164. Median values were 0.942 and 1.008, respectively, which were similar to the means and significantly different from each other.

Vdp/Va values. Use of the correction equation (Equation 5) to adjust Vsp to an estimated Vdp had little effect in the standard treatment arm, as the mean URR in the standard arm was very close to that level where the two-pool model equations predicted that Vsp = Vdp. However, the application of the correction equation caused a significant downward adjustment of Vsp in the high-treatment arm. The Vdp/Va ratios in the two treatment arms were 0.959 ± 0.148 and 0.979 ± 0.175, respectively (P = NS; Fig. 2, right panel). Median values were 0.941 and 0.960 in the standard and high arms, respectively.

Other treatment parameters

These are listed in Table 1.

Comparing within treatment Vsp values at F4

At the fourth month into the trial, in addition to the predialysis and postdialysis samples, a one-hour blood sample was also obtained, which permitted computation of unadjusted Vsp both at this time point and at the end

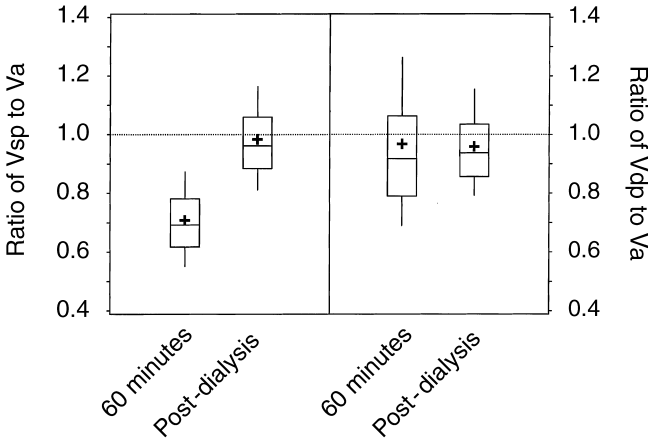

Fig. 3. (Left panel) Vsp/Va ratios at one hour vs. postdialysis. (Right panel) Vdp/Va ratios at one hour vs. postdialysis.

of dialysis. For the one-hour analysis, data from patients in the standard and high goal groups were pooled. At F4, the mean URR based on the predialysis and postdialysis BUNs was 0.712. The mean Vsp/Va ratio was 0.995 ± 0.155, and the mean Vdp/Va ratio was 0.970 ± 0.163.

At one hour into the treatment, the mean URR was 0.410 ± 0.068, and the mean Vsp/Va ratio was only 0.708 ± 0.139. Using the correction formula to compute an estimate Vdp yielded a Vdp/Va ratio of 0.968 ± 0.322, a value that was not significantly different from the Vdp/Va ratio measured using the postdialysis BUN (Fig. 3).

DISCUSSION

In urea modeling, the computation of the modeled V can be of clinical value. In any given patient, the true TBW can differ substantially from the anthropometric estimate of urea distribution volume (Va). This is why the mean modeled V, once established, is useful in following the adequacy of dialysis over time. The ratio of the modeled to anthropometric V is also useful. A ratio that is far away from 1.0 indicates that perhaps some of the treatment assumptions (that is, dialyzer clearance, delivered blood flow, and delivered session length) may need to be verified.

The modeled V is not a major factor in the computation of the Kt/V, because in a fixed volume model, the Kt/V is independent of V. In the variable volume model, the modeled V will have only a small effect on Kt/V. Hence, simplified equations that correct for ultrafiltration are useful in estimating the delivered Kt/V. However, it is well established that formal urea kinetics offer substantial advantages in terms of dialysis prescription and quality assurance.

The "gold standard" methodology, variable volume single-pool urea kinetics, which has been recommended as a standard by DOQI, has this little wrinkle in it: The modeled V may change in a given patient when the amount of dialysis given markedly increases or decreases. Put more precisely, modeled Vsp is a function of the URR. The effect of the URR on Vsp was previously worked out in a theoretical sense, and a correction formula was devised. The correction factor is derived from the URR and the ratio BUNpost/BUNeq, which is approximately a function of the dialysis rate, Kd/V [4].

In this study, the correction formula was tested using the HEMO patient data. The correction formula was based on a simplified fixed-volume, double-pool model of urea kinetics that ignored urea generation and ultrafiltration. The clinical testing of the correction equation as reported here shows that the effects of ultrafiltration and urea generation (that are necessary for precise and accurate double-pool modeling) do not substantially affect the basic predictions of the correction formula. The formula predicts that Vsp is equal to the true V (Vdp) at a URR of approximately 67%, that Vsp is less than Vdp at lower levels of URR, and that Vsp is greater than Vdp at higher levels of URR.

In the National Institutes of Health HEMO Study, both treatments are not too distant from a URR of 67%. In fact, in the standard goal arm, the mean URR is very close to 67%, the level at which Vsp is expected to equal Vdp. In the high goal treatment arm, the mean URR is approximately 75%, a level at which Vsp is predicted to exceed Vdp by approximately 5%, given the Kd/V (dialysis rates) values used in the HEMO Study.

These small changes in V were detected easily in the HEMO Study because of the large numbers of patients involved. Whereas a 5% departure in Vsp from Vdp would seem to be of little clinical significance, in the HEMO Study, this error caused a noticeable error in the initial dialysis prescription until the problem was identified and corrected. In the HEMO Study, the high-goal prescription is applied initially to demonstrate feasibility and patient acceptance of the dialysis time, which was required to be increased in many cases. In the course of several modeled dialyses, a value for Vsp was determined repeatedly, and the average value was used in subsequent modelings. When the patients were randomized to either stay on the high-goal or the treatment was adjusted to the standard goal (eKt/V = 1.05, or a URR of approximately 67%), prescriptions for the standard goal overestimated the delivered spKt/V and eKt/V; the patients randomized to the standard goal appeared to have "shrunk" by approximately 5%, resulting in a higher than expected level of delivered therapy. The application of the correction formula for Vsp/Vdp solved the problem and resulted in similar ratios of delivered to prescribed Kt/V in the two treatment arms.

Because the median URR in the United States is close to 67% (spKt/V = 1.3) [6], V derived from single-pool kinetic modeling and simplified formulas designed to

mimic the single-pool model is generally close to the anthropometrically derived TBW. It is important to realize that this will not be the case with, for example, daily hemodialysis regimens, where the URR values of 0.35 to 0.40 may be the rule or for early start dialysis where lower Kt/V targets may be sought. The correction formula suggests that Vsp will be substantially lower than the true V in these circumstances.

The Vsp/Vdp correction formula is important in other areas as well, for example, when comparing volumes derived from blood and dialysate side modeling. On the other hand, we found that the variance of repeated measures of Vdp within patients using the same prescription was greater than the variance of Vsp. It appears that the reason for the greater variance of Vdp is that variations in the URR add to the variance of Vsp, often doubly increasing its variance. Thus, for patients on a fixed prescription, it may be more practical to follow Vsp instead of converting each measure to a Vdp to adjust dialysis time and flow rates. However, Vdp should be used when a marked change in the prescribed dialysis dose is contemplated.

In summary, these data from the NIH HEMO Study, using a variable volume model of urea kinetics that includes urea generation, validates the kinetically-derived correction formula for Vsp/Vdp based on a fixed volume model with no urea generation. This formula should be used when making changes in the dialysis prescription when a marked alteration of the target URR is planned.

Reprint requests to John Daugirdas, M.D., Department of Medicine, Nephrology M/C 793, University of Illinois College of Medicine, 1737 West Polk Street, Chicago, Illinois 60612, USA.
E-mail: jtdaugir@uic.edu

APPENDIX

Abbreviations are: BUN, blood urea nitrogen; BUNeq, equilibrated post-dialysis BUN; eG, urea generation rate; eKt/V, equilibrated dialysis dose; F4, month 4; Fdp, blood urea nitrogen (BUN) post/BUNeq; G, urea generation rate; Qb, dialyzer blood flow rate; Qd, blood flow rate; Kd, dialyzer clearance; KoA, mass transfer area coefficient; K/V, clearance per volume; spKt/V, single pool dialysis dose; t, treatment time; TBW, total body water; Td, dialysis time; URR, urea reduction ratio; V, urea distribution volume; Va, anthropometric volume; Vdp, volume derived from double-pool kinetics; Vsp, volume derived from single-pool kinetics.

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