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Effect of a two compartment distribution on apparent urea distribution volume

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Blood-based urea kinetic modeling (UKM) permits estimation of the urea distribution volume V that may be compared with the anthropometrically-predicted volume to determine if the kinetic modeling results are plausible. Various confounding factors may cause differences between the true distribution volume and that measured by UKM. During hemodialysis, three principal mechanisms are likely to contribute to an effective multicompartmental distribution of urea: access recirculation, cardiopulmonary recirculation and distribution of urea between intra- and extracellular, and/or low and high blood flow, compartments [1]. The effect of each of these mechanisms is to reduce the efficiency of dialysis by lowering the intradialytic serum blood urea nitrogen (BUN) profile. After dialysis, the serum BUN level will rebound with different time scales for access recirculation (over a period of approximately 10 seconds [1]), cardiopulmonary recirculation (typically over a period of 2 min [2]), and the compartmental effects (over a period of 30 to 60 min [3, 4]).

Ideally blood drawn for urea kinetic modeling should be drawn after all three rebounds have occurred, 30 to 60 minutes post-dialysis. If this is done, single-pool modelling based on the expected dialyzer urea clearance estimate will give an inflated estimate of the urea distribution volume. Single pool modeling assumes that the dialyzer clearance results in a monoexponentially decreasing plasma urea profile from the pre- to the post-dialysis BUN samples. Because of the recirculation/compartmental effects noted above effective dialyzer clearance will be less than that expected (K), and this is mathematically equivalent to an increased urea distribution volume V for a given exponent K/V.

When blood is sampled before rebound has occurred, the situation is more complex; single-pool UKM can underestimate, correctly estimate, or overestimate the true urea distribution volume, depending on the level of urea reduction that has occurred [1, 5]. This is because two counteracting effects are in play [6]. On the one hand, the fraction of urea distribution volume cleared (Kt/V) is overestimated, and this causes an underestimation of the urea distribution volume for the expected V value. On the other hand, the intradialytic urea profile is still lower than that estimated by a monoexponential curve from the predialysis BUN to the unequilibrated post-dialysis BUN. The latter effect overestimates the amount of urea removed and overestimates V for the expected K value.

A very similar problem occurs with access recirculation (AR), where AR causes a decrease in the intradialytic urea profile presented to the dialyzer. The effect of AR on V was recently analyzed in detail by Daugirdas, Schneditz and Leehey [5], and it was shown that, when the postdialysis blood sample is drawn before the access rebound has occurred, the effect of AR on V depends on the urea reduction ratio (URR), and is neutral at a URR value of about 65 to 70%. In that study it was recognized that a similar analysis could be applied to cardiopulmonary recirculation and to compartment effects, though the effect of urea compartmentalization on V was not developed in detail.

The purpose of the present study was to analyze how closely the single-pool V (determined from single-pool UKM based on a postdialysis BUN sample obtained promptly after the end of dialysis and an assumed value for K) corresponds to the "true" or multicompartment modeled V, which theoretically should be similar to the patient's total body water volume. In the analysis it has been assumed that the effects of access recirculation, the first phase of rebound, have been obviated by drawing the post-dialysis sample after a 10- to 15-second slow flow period, thereby clearing the line of possibly recirculated blood.

Analysis

The following analysis builds on that previously reported [4] using a fixed volume double-pool urea kinetic model assuming no urea generation. It is assumed that urea is distributed between an intracellular and an extracellular compartment, of fixed volumes V_1 and V_2, respectively. Neglecting urea generation, ultrafiltration, access and cardiopulmonary recirculation, and assuming that diffusion is the principal transport mechanism between the two compartments with mass transfer coefficient X (equivalent to the Kc previously described by others), then time t following the start of a hemodialysis session of duration T using a dialyzer of clearance K, the intra- and extracellular urea concentrations C_1, C_2 are given by

$$C_1 = \alpha_1 A e^{-\lambda_+ t} + \alpha_2 B e^{-\lambda_- t} \quad \text{(Eq. 1)}$$

$$C_2 = A e^{-\lambda_+ t} + B e^{-\lambda_- t} \quad \text{(Eq. 2)}$$

where α_1, α_2, A, B, λ_+, λ_- are constants that are functions of K, X, V_1, V_2 and the initial pre-dialysis blood urea concentration

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$C_2(0)$ [4]. In practice $\lambda_+ >> \lambda_-$ [4], which means that during the later stages of dialysis the variation in blood urea concentration C_2 is described by a single exponential (from Eq. 2) thus,

$$C_2(t) \simeq Be^{-\lambda_- t} \quad \text{(Eq. 3)}$$

This model equation is very significant because it is describing a process whereby during this later phase, hemodialysis proceeds as if the urea is being cleared through a dialyzer of clearance K from a single compartment with effective volume V_{eff} where

$$V_{eff} = \frac{K}{\lambda_-} \quad \text{(Eq. 4)}$$

An equivalent interpretation of this phase is that urea is being cleared from a distribution volume V, but with a reduced effective dialyzer clearance K_{eff}, where

$$K_{eff} = \lambda_- V \quad \text{(Eq. 5)}$$

Previous analysis [4] shows that for typical parameter values

$$\lambda_- \simeq \frac{K}{V}\left[1 - \frac{\epsilon V_1^2}{V^2}\right] \quad \text{(Eq. 6)}$$

$$B \simeq C_2(0)\left[1 - \frac{\epsilon V_1^2}{V^2}\right] \quad \text{(Eq. 7)}$$

where $\epsilon = K/X$. From equations 4, 5 and 6

$$V_{eff} = \frac{V}{\left[1 - \frac{\epsilon V_1^2}{V^2}\right]} \quad \text{(Eq. 8)}$$

$$K_{eff} = K\left[1 - \frac{\epsilon V_1^2}{V^2}\right] \quad \text{(Eq. 9)}$$

The preceding early phase of the hemodialysis treatment represents a transient stage during which the effective volume of urea distribution increases from $V (= V_1 + V_2)$ to V_{eff}, and blood urea concentration variation is then described by two exponentials reflecting the contribution of two compartments. Following hemodialysis, the post-dialysis rebound in blood urea concentration reflects the process of re-equilibration during which the effective urea distribution volume decreases to $(V_1 + V_2)$.

Thus, after a treatment of duration T, from equations 3 and 8

$$C_2(T) \simeq C_2(0)Fe^{-\frac{FKT}{V}} \quad \text{(Eq. 10)}$$

where

$$F = \left[1 - \frac{\epsilon V_1^2}{V^2}\right] \quad \text{(Eq. 11)}$$

Effect on estimate of urea volume using single pool model

Using a single pool kinetic model in which the same dialyzer urea clearance K is assumed, the end-dialysis blood urea concentration is given by

$$C_2(T) = C_2(0)e^{-\frac{KT}{V_{sp}}} \quad \text{(Eq. 12)}$$

where V_{sp} is the effective urea distribution volume given by the single pool model. The urea distribution volume calculated from this model using measured pre- and immediate post-dialysis blood urea concentrations will then be

$$V_{sp} = \frac{KT}{\log_e\left[\frac{C_2(0)}{C_2(T)}\right]} \quad \text{(Eq. 13)}$$

However, the true urea distribution volume estimate V is given from the two-pool compartment model, equation 10, by

$$V = \frac{FKT}{\log_e \frac{FC_2(0)}{C_2(T)}} \quad \text{(Eq. 14)}$$

From equations 13 and 14,

$$\frac{V_{sp}}{V} = \frac{\log_e\left[\frac{FC_2(0)}{C_2(T)}\right]}{F\log_e\left[\frac{C_2(0)}{C_2(T)}\right]} \quad \text{(Eq. 15)}$$

Assume that $\epsilon \approx 0.4$ and that $V_1/V \approx 0.67$ [4]. Then, from equation 7, $F \approx 0.82$. Figure 1 shows a plot of V_{sp}/V as a function of the urea reduction ratio (URR) for $F = 0.82$ as well as for other values for F, where

$$URR = 100\left(1 - \frac{C_2(T)}{C_2(0)}\right) \quad \text{(Eq. 16)}$$

From Figure 1 it is clear that, below a URR of about 70%, $V_{sp}/V < 1.0$. Above a URR of 70%, $V_{sp}/V > 1.0$. The value of Kt/V to which this corresponds may be estimated by using the approximate formula [7, 8]

$$\frac{KT}{V} = -1.18\log_e R \quad \text{(Eq. 17)}$$

where

$$R = \left(1 - \frac{URR}{100}\right) \quad \text{(Eq. 18)}$$

Thus, at a Kt/V value of about 1.3, the single-pool and double-pool volume estimates coincide.

While this analysis has proceeded assuming diffusion to be the principal transport mechanism between the two pools, a flow-based model [9, 10] would yield similar results given the similarity between the form of the equations describing both the diffusion and flow based models. The introduction of a variable pool model and urea generation has little impact on the results, as the relationship between V_{sp}/V and the URR is primarily concentration-dependent [5, 11].

In the above example it was assumed that, $\epsilon = 0.4$ and F was therefore estimated to be 0.82. However, the variation of F with K/V may be estimated by the following approximations; from previous work [4] the post-dialysis equilibrium blood urea concentration is given by

$$C_{2eqm} = C_2(0)e^{-\lambda_- T} \quad \text{(Eq. 19)}$$

From equations 6, 10, 18 and 19

$$R_{eq} = \frac{R}{F} \quad \text{(Eq. 20)}$$

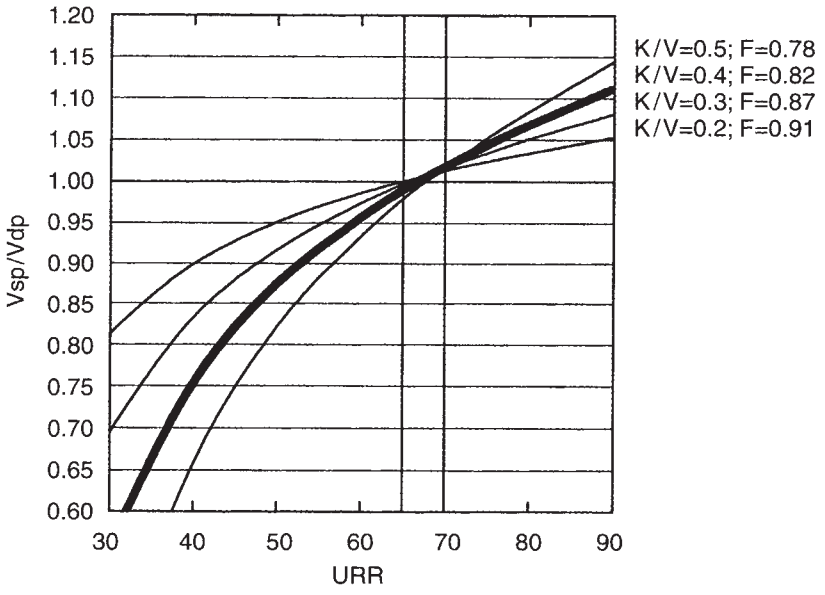

Fig. 1. *Relationship between Vsp/Vdp and URR is shown for various levels of K/V (expressed in units of single-pool Kt/V units delivered per hour) and F.* It can be seen that, regardless of K/V or F, Vsp/Vdp approaches unity at a URR of about 67%. Compare this with a similar analysis of the effect of access recirculation on apparent urea distribution volume published elsewhere [5].

and

$$\frac{C_2(T)}{C_{2eqm}} = F \qquad \text{(Eq. 21)}$$

where $R_c = C_{2eqm}/C_2$ (0). Similarly, we may estimate the Kt/Vs derived from the unequilibrated and equilibrated post-dialysis samples from

$$\frac{KT}{V} = -1.18\log_e R$$
$$\frac{eKT}{V} = -1.18\log_e \frac{R}{F} \qquad \text{(Eq. 22)}$$

From the rate equation [12] it is known that:

$$\frac{eKT}{V} = \frac{KT}{V_{sp}} - 0.6\frac{K}{V_{sp}} + 0.03 \qquad \text{(Eq. 23)}$$

Therefore, after simplification of Equations 20 to 23

$$F = 1 - 0.44\frac{K}{V_{sp}} \qquad \text{(Eq. 24)}$$

Equation 24 can be used with Equation 15 to estimate the volume ratio at any level of R and K/V.

Figure 1 also shows how V_{sp}/V changes as a function of the URR for various levels of K/V. It can be seen that at a single-pool URR of about 67%, corresponding to a single-pool Kt/V of about 1.3, Vsp/V is 1.0, regardless of the level of K/V or F.

Discussion

In the majority of studies reported to date, with a mean Kt/V value in the range of 1.0 to 1.4, the single pool modeled V was similar to the anthropometric V [13]. The reason is that V_{sp}/V in this Kt/V range should be similar to 1.0. However, if one is analyzing a wide range of Kt/V values, and analyzing the single pool modeled to anthropometric volume ratios, say 0.6 to 2.0, one would expect that the single pool volume should underestimate anthropometric V in the low Kt/V range (< 1.0) and overestimate anthropometric V in the high Kt/V range (> 1.5). A modeled/anthropometric volume ratio close to 1.0 in patients receiving a Kt/V of 0.8, for example, might actually reflect an overestimation of dialyzer clearance and thus of V_{sp}. Hence, one implication of the present data is that if the ratio of single-pool modeled V to anthropometric V is used to assess dialyzer clearance and other components of dialysis therapy, the relation between V_{sp}/V and URR must be accounted for. Likewise, when comparing urea distribution volumes computed using blood versus dialysate side methods of urea modeling, one should not expect that Vsp computed from blood sided methods will equal the V from dialysate side methods, unless the mean URR is close to 67%.

An important clinical implication of these data relates to the circumstances in which a significant change in a patients dialysis dose is proposed; for example, assume that one wants to increase a patient from a single-pool Kt/V of 1.0 to 1.6 (URR from about 57 to 75%). If the patient's Vdp is around 40, and the dialyzer clearance is about 227 ml/min, one would be achieving a single pool Kt/V of 1.0 in about 168 minutes, which would yield a K/V of about 0.357 units/hr, and an F of about 0.843 from Equation 24. To achieve the new Kt/V of 1.6, one would expect that the increase in dialysis time would be 1.6 × 168 minutes = 268 minutes, or +100 minutes. In fact, at this level of K/V, the apparent Vsp at a Kt/V of 1.0 is really 38.1 liters, since the Vsp/Vdp ratio at a URR of 57% (which corresponds to a Kt/V single pool of 1.0) is about 0.95 (Fig. 1). At the new single-pool Kt/V of 1.6, however, the Vsp/Vdp ratio is now about 1.035, and the patient's Vsp should increase to 41.3 liters. As a result, the required dialysis time becomes 294 minutes instead of 268 minutes, and the increase required is +126 minues rather than +100 minutes, which is 26% higher than predicted. Thus, although the Vsp/Vdp correction appears to be small, it can have a substantial impact with regard to dialysis prescription, especially when the

initial prescription is for single-pool Kt/V levels at 1.0 or lower (such as in patients with substantial residual renal function).

Furthermore, as shown in Figure 1, because the Vsp/Vdp ratio is a function of K/V, at high dialysis efficiency rates the change in the ratio will be even more pronounced, and the required increase in dialysis time will be even longer.

In summary, an analysis is presented whereby apparent single pool urea volume can be converted to double-pool urea volume based on dialysis efficiency (K/V) and the URR. These corrections can impact significantly on the prescription of dialysis, especially when large changes in URR are proposed.

A similar analysis has been used in interpretation of data from the ongoing NIH HEMO trial, where Equation 15 was evaluated clinically [14]. These data, presented in abstract form at the 1996 meeting of the American Society of Nephrology, will be published in a separate communication.

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