Quantifying the Effect of Changes in the Hemodialysis Prescription on Effective Solute Removal with a Mathematical Model

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Abstract. One potential benefit of chronic hemodialysis (HD) regimens of longer duration or greater frequency than typical three-times-weekly schedules is enhanced solute removal over a relatively wide molecular weight spectrum of uremic toxins. This study assesses the effect of variations in HD frequency (F: per week), duration (T: min per treatment), and blood/dialysate flow rates (Q_B/Q_D: ml/min) on steady-state concentration profiles of five surrogates: urea (U), creatinine (Cr), vancomycin (V), inulin (I), and β2-microglobulin (β2M). The regimens assessed for an anephric 70-kg patient were: A (standard): F = 3, T = 240, Q_B = 350, Q_D = 600; B (daily/short-time): F = 7, T = 100, Q_B = 350, Q_D = 600; C/D/E (low-flow/long-time): F = 3/5/7, T = 480, Q_B = 300, Q_D = 100. HD was simulated with a variable-volume double-pool model, which was solved by numerical integration (Runge–Kutta method). Endogenous generation rates (G) for U, Cr, and β2M were 6.25, 1.0, and 0.17 mg/min, respectively; constant infusion rates for V and I of 0.2 and 0.3 mg/min, respectively, were used to simulate middle molecule (MM) G values. Intercompartment clearances of 600, 275, 125, 90, and 40 ml/min were used for U, Cr, V, I, and β2M, respectively. For each solute/regimen combination, the equivalent renal clearance (EKR: ml/min) was calculated as a dimensionless value normalized to the regimen A EKR, which was 13.4, 10.8, 6.6, 3.7, and 4.8 ml/min for U, Cr, V, I, and β2M, respectively. For regimens B, C, D, and E, respectively, these normalized EKR values were U: 1.04, 0.96, 1.58, and 2.22; Cr: 1.03, 1.08, 1.80, and 2.55; V: 1.06, 1.32, 2.21, and 3.12; I: 1.05, 1.54, 2.57, and 3.62; β2M: 1.00, 1.27, 1.73, and 2.19. The extent of post-HD rebound (%) was highest for regimens A and B, ranging from 16% (urea) to 50% (inulin), and lowest for regimen E, ranging from 6% (urea) to 28% (β2M). The following conclusions can be made: (1) Relative to a standard three-times-weekly HD regimen of approximately the same total (weekly) treatment duration, a daily/short-time regimen results in modest (3 to 6%) increases in effective small solute and MM removal. (2) Relative to a standard three-times-weekly HD regimen, a three-times-weekly low-flow/long-time regimen results in comparable effective small solute removal and progressive increases in MM and β2M removal. A daily low-flow/long-time regimen substantially increases the effective removal of all solutes.

The solute removal capabilities of chronic hemodialysis (HD) and related therapies used for end-stage renal disease (ESRD) patients differ from those of the native kidney in several respects. One important difference is the intermittent nature of HD, which results in intradialytic compartmentalization of solutes and limitation of effective solute removal (1), regardless of solute molecular weight (MW). During HD, direct removal of a particular solute can only occur from that portion of its volume of distribution that actually perfuses the dialyzer, and sequestration of solute occurs in the remaining volume of distribution. Solute compartmentalization involves an interplay between dialyzer solute clearance and patient/solute parameters, such as compartment volumes and intercompartment mass transfer resistances (2). Even if solute removal from a perfused compartment is relatively efficient during an intermittent therapy, overall (effective) solute removal may be limited by slow intercompartment mass transfer. This limitation is manifested clinically by the posttreatment rebound in solute concentration (3), the magnitude of which is directly related to the extent of intradialytic compartmentalization.

Chronic HD schedules that differ significantly from traditional three-times-weekly regimens have recently been advocated (4–7). Several aspects of these alternative schedules differ from traditional regimens, including flow rates, duration, and frequency. Although clinical outcomes have been reported to be excellent (5–7), the effective solute removal capabilities of these therapies have not been assessed rigorously, especially...
compared with those of more traditional regimens. Therefore, we have developed a two-compartment model designed to quantify differences between traditional and alternative HD regimens in removal profiles for solutes over a wide MW spectrum. The quantitative basis for this model is the equivalent renal clearance (EKR), recently formulated by Casino and Lopez (8).

Materials and Methods

A diagram of the model is shown in Figure 1 (9). The total volume of distribution for a particular solute had two components: a perfused compartment, to which the dialyzer has access, and a nonperfused compartment. Mass transfer between the two compartments was defined by $K_{IC}$ (ml/min), the intercompartment clearance. Ultrafiltration requirements were based on an assumed water generation rate of 1 L/d. It was assumed that solute generation ($G$: mg/min) and nonrenal clearance ($K_{NR}$: ml/min) apply only to the perfused compartment, whereas ultrafiltration occurs from both compartments such that the ratio of the compartment ultrafiltration rates is the same as that of the compartment volumes. Although vancomycin has a nonrenal clearance of approximately 5 ml/min in ESRD patients, this was not incorporated into the model to allow for greater differentiation of the various regimens. For $\beta_2$-microglobulin ($\beta2M$), an assumed nonrenal clearance of 3 ml/min was used (9). Simulations were performed for an anephric ESRD patient of dry weight 70 kg.

Five uremic surrogate molecules with a broad MW spectrum were investigated (Table 1). Three different surrogate categories were assessed: low MW nitrogenous waste products (urea and creatinine), middle molecules (vancomycin and inulin), and low MW proteins ($\beta2M$). Although vitamin $B_{12}$ is used to characterize in vitro middle molecule dialyzer transport, it is not useful as an in vivo surrogate due to extensive protein binding (10). On the other hand, vancomycin has a MW very similar to that of vitamin $B_{12}$ and is frequently used in ESRD patients, making it a much more valid middle molecule surrogate (11). The total volume of distribution ($V_2$: 40 L) for urea, creatinine, and vancomycin was typical body water (TBW) (12–15), with the extracellular water (ECW) and intracellular water (ICW) as the perfused and nonperfused compartments, respectively. For inulin and $\beta2M$, the $V_1$ was ECW (13.3 L), with intravascular water and interstitial water as the perfused and nonperfused compartments, respectively (9,16–20). Estimates for intercompartment clearances were derived from data previously reported in the HD and pharmacokinetic literature (1,9,16,21–26). Endogenous solute generation rates for urea, creatinine, and $\beta2M$ were typical of those reported previously for a 70-kg ESRD patient (14,19–21,26–29), whereas endogenous generation of vancomycin and inulin was simulated by a continuous infusion of drug. For all solutes, generation rate was assumed to be constant.

The assessed HD regimens are shown in Table 2. All regimens were assumed to be symmetrical, i.e., treatments were equally spaced such that the interdialytic time intervals and, therefore, predialysis concentrations were equal. Clearances for urea and inulin, as representative solutes having one of the volumes of distribution described above, are shown in addition to the therapy parameters. Being a typical in-center high-flux HD schedule, regimen A served as a control to which the alternative regimens were compared. Regimen B,

### Table 1. Solute characteristics

<table>
<thead>
<tr>
<th>Solute (MW)</th>
<th>$G$ (mg/min)</th>
<th>$K_{IC}$ (ml/min)</th>
<th>$K_{oA}$ (mg/min)</th>
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<tr>
<td>Urea (60)</td>
<td>6.25</td>
<td>600</td>
<td>494</td>
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<tr>
<td>Creatinine (113)</td>
<td>1.0</td>
<td>275</td>
<td>350</td>
</tr>
<tr>
<td>Vancomycin (1448)</td>
<td>0.2</td>
<td>125</td>
<td>149</td>
</tr>
<tr>
<td>Inulin (5200)</td>
<td>0.3</td>
<td>90</td>
<td>81</td>
</tr>
<tr>
<td>$\beta2M$ (11,800)</td>
<td>0.17</td>
<td>40</td>
<td>32</td>
</tr>
</tbody>
</table>

$^a$ MW, molecular weight; $\beta2M$, $\beta_2$-microglobulin.

### Table 2. Hemodialysis regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Frequency (per week)</th>
<th>Time (min)</th>
<th>$Q_B/Q_D$ (ml/min)</th>
<th>$K_{urea}$ (ml/min)</th>
<th>$K_{inulin}$ (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3</td>
<td>240</td>
<td>350/600</td>
<td>231</td>
<td>75</td>
</tr>
<tr>
<td>B</td>
<td>7</td>
<td>100</td>
<td>350/600</td>
<td>231</td>
<td>75</td>
</tr>
<tr>
<td>C</td>
<td>3</td>
<td>480</td>
<td>300/100</td>
<td>101</td>
<td>56</td>
</tr>
<tr>
<td>D</td>
<td>5</td>
<td>480</td>
<td>300/100</td>
<td>100</td>
<td>54</td>
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<td>E</td>
<td>7</td>
<td>480</td>
<td>300/100</td>
<td>99</td>
<td>53</td>
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</tbody>
</table>

Figure 1. Diagrammatic representation of the two-compartment model. See text and appendices for explanation of symbols.
recently proposed as a more efficient way to remove urea (7), used the same flow rates as in regimen A, but for a shorter duration and higher frequency. In the remaining regimens, a relatively low $Q_D$ resulted in nearly complete saturation of the effluent dialysate with respect to urea. The three-times-weekly low-flow schedule (regimen C) bears similarities to that described by Charra et al. (4), although there are differences in membrane flux and dialysate flow rate between the two regimens. The daily low-flow schedule (regimen E) was similar to that currently used by Pierratos (5).

The steady-state compartment concentration profile for a particular solute was determined by solving a series of mass balance equations shown in Appendix 2. An initial estimate of the predialysis solute concentration was provided to the computer model. The model then iteratively solved the mass balance equations, yielding compartment concentration profiles for a complete dialysis cycle (Dialysis cycle = Intradialytic period + Interdialytic period) by use of a fourth-order Runge–Kutta technique with a 1-min time increment (36). These iterations resulted in convergence of the predialysis solute concentration on a stable (i.e., steady-state) value. Six cycles were adequate time for this convergence to occur for all regimens.

The rebound period was the time required posttreatment for the two compartment solute concentrations to become equal (i.e., equilibrate). Percent rebound was based on perfused compartment concentrations:

\[
\text{Percent Rebound} = \left[\frac{C_{EQ} - C_T}{C_T}\right] \times 100\%,
\]

where $C_{EQ}$ and $C_T$ are the equilibrated and immediate postdialysis concentrations, respectively.

From the steady-state compartment concentration profiles, a time-averaged concentration (TAC) was obtained for a specific solute/regimen combination. The TAC was a “whole-body” parameter that accounted for concentration gradients existing between the two compartments during the intradialytic and postdialytic rebound periods. A solute’s TAC in both compartments of its total distribution volume was determined such that both the intradialytic and interdialytic profiles were treated as linear:

\[
TAC = \left[\frac{C_0 + C_T}{T_D} + \frac{C_T + C_{EQ}}{T_R} + \frac{C_{EQ} + C_0}{T_{ID}}\right]/2(T_D + T_R + T_{ID}),
\]

where $C_0$ is the predialysis concentration, and $T_D$, $T_R$, and $T_{ID}$ are the duration of the dialytic, rebound, and interdialytic periods, respectively. The whole body TAC was then determined by summing the individual compartment TAC values, weighted for compartment volume. With TAC (and G) known, EKR could then be determined as (8):

\[
EKR (\text{ml/min}) = G (\text{mg/min})/\text{TAC (mg/ml)}.
\]

Results
Concentration Profiles
In Figure 2, compartment concentration profiles for representative solutes with either a TBW or ECW total distribution volume (urea [Figure 2a] and inulin [Figure 2b], respectively) are shown for regimen A. These profiles show the intradialytic and immediate postdialytic (rebound) periods. The salient features of the urea profiles are the biexponential character of the perfused compartment curve and an intercompartment concentration gradient during dialysis, which is subsequently dissipated in the rebound phase. Although the general features of the inulin profiles are similar to those for urea, distinct differences are readily evident. First, the perfused compartment profile has a much more pronounced biexponential character. The more significant intercompartment inulin concentration gradient that develops during dialysis is a second major difference. As a result, the extent of post-HD rebound is significantly greater for inulin than urea.

These differences can be explained by assessing the relationship between dialyzer clearance, intercompartment clearance, and compartment volumes for each solute. First, the relative rates at which the perfused and nonperfused compartments are cleared are significantly different for the two solutes. The ratio of intercompartment clearance to dialyzer clearance ($K_{IC}/K_D$) for urea is 2.6 (600/231), whereas the same parameter...
for inulin is only 1.2 (90/75). Another factor is the relative compartment volumes for the two solutes. For urea, the ratio of perfused compartment volume to total $V_D$ is 1:3, whereas the same ratio for inulin is 1:4. Therefore, expressed as a function of total $V_D$, the volume to which the dialyzer has access for solute removal is relatively greater for urea. Finally, the absolute volumes from which extracorporeal clearance occurs for the two solutes also help to explain the differences. Although dialytic clearance of inulin is significantly less than that of urea (75 and 231 ml/min, respectively), the efficiency ($K_D/V_P$) with which the perfused compartment is cleared is higher for inulin than for urea (1.36 and 1.05 h$^{-1}$, respectively). Thus, differences in the kinetic behavior of urea and inulin can be explained by the latter’s combination of efficient removal from a small perfused compartment and slow intercompartment mass transfer.

For the same representative solutes, the qualitative differences in the steady-state removal kinetics between regimens using relatively high flow rates (regimens A and B) and low flow rates (regimen C) are shown in Figure 3. Perfused compartment concentration profiles over a time period corresponding to one complete treatment cycle (56 h) for the three-times-weekly regimens (A and C) are shown. For urea, the three regimens achieve the same approximate TAC (vide infra: see Table 4) but the profiles differ in certain respects. A relatively steep intradialytic blood urea nitrogen decline for the high-flow regimens is associated with a more pronounced rebound than for the low-flow regimen, in which the rate of urea removal is slower. The differences in posttreatment rebound between the high-flow and low-flow regimens are even more pronounced for inulin. As discussed above, these results can be explained by differences in the relative rates of intercompartment and dialyzer clearance and the efficiency of solute removal from the perfused compartment. For example, the urea $K_{IC}/K_D$ ratio is 2.6 for regimens A and B and 6.0 for regimen C, whereas the urea efficiency factor ($K_D/V_P$) is 1.05 h$^{-1}$ for regimens A and B and 0.45 h$^{-1}$ for regimen C.

### Postdialysis Solute Concentration Rebound

The extent (percentage) of post-HD solute concentration rebound for all regimens is shown in Table 3. For solutes with a TBW distribution, two general observations can be made. First, as discussed above, rebound is more significant for the high-flow regimens (A and B) than the low-flow regimens (C, D, and E). Second, rebound in the two high-flow regimens is similar while it progressively decreases as therapy frequency increases in the low-flow regimens.

For solutes with an ECW volume of distribution, rebound trends are less predictable. For inulin, rebound in the high-flow regimens (approximately 50%) is the highest of all solute/regimen combinations assessed. However, the direct correlation seen for solutes with a TBW distribution between solute MW and rebound (vide supra) is not observed for inulin and $\beta 2M$ within a specific regimen. For the low-flow regimens, the percent rebound values for these solutes are generally comparable, whereas the rebound of the larger solute $\beta 2M$ is actually substantially lower (by approximately 10 to 20%) than that of inulin for both of the high-flow regimens. These results can be explained primarily by the relatively greater difference in dialyzer clearances than in intercompartment clearances between

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Urea</th>
<th>Creatinine</th>
<th>Vancomycin</th>
<th>Inulin</th>
<th>$\beta 2M$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>15.8</td>
<td>31.3</td>
<td>41.1</td>
<td>49.8</td>
<td>45.3</td>
</tr>
<tr>
<td>B</td>
<td>18.5</td>
<td>34.5</td>
<td>36.1</td>
<td>49.6</td>
<td>38.3</td>
</tr>
<tr>
<td>C</td>
<td>7.4</td>
<td>15.7</td>
<td>28.1</td>
<td>32.5</td>
<td>36.6</td>
</tr>
<tr>
<td>D</td>
<td>6.4</td>
<td>13.6</td>
<td>24.7</td>
<td>26.8</td>
<td>32.3</td>
</tr>
<tr>
<td>E</td>
<td>5.5</td>
<td>11.6</td>
<td>21.6</td>
<td>21.9</td>
<td>27.8</td>
</tr>
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</table>
the two solutes. Indeed, the dialyzer clearance of inulin for these regimens is approximately 2.5-fold greater than that of β2M, whereas the same ratio for intercompartment clearances is only 2.25. That dialyzer clearance occurs from a compartment with a small absolute volume, only one-third the size of the compartment from which intercompartment clearance occurs, also accounts for these rebound results.

**Equivalent Renal Clearances**

TAC and EKR values for modeled solutes are given in Tables 4 and 5, with the results for small solutes (Table 4) and middle and large molecules (Table 5) shown separately. In addition, for each solute/regimen combination, the EKR normalized to regimen A EKR value appears in Table 6. For urea, comparisons are made between EKR, which quantifies effective solute removal by incorporating TAC, and weekly (single-pool) Kt/V, a purely clearance-based measurement that provides no information on actual solute removal. A divergence between these two parameters is observed for regimens A and B, which differ significantly in both frequency and duration of therapy. Therefore, these data reinforce previous arguments (37,38) that purely clearance-based measurements cannot be used to compare disparate therapies.

The data in Table 4 also demonstrate the primary importance of flow rates in determining diffusive small solute clearances. For the high-flow regimens, in which the dialysate flow rate is 600 ml/min, EKR values for urea are approximately 25% greater than those for creatinine. However, a similar comparison for the low-flow regimens, in which the dialysate flow rate is only 100 ml/min, yields a much smaller 8 to 9% difference. A similar discrepancy in clearances of these two solutes (39) has been reported between continuous ambulatory peritoneal dialysis and automated peritoneal dialysis, two therapies that also use significantly different dialysate flow rates.

Although the total weekly treatment time of regimen C (24 h) is approximately twice that of regimens A and B (both about 12 h), the small solute EKR values for the three schedules are very similar (Table 4). However, for solutes in the middle and large molecule categories, regimen C provides effective clearances that are 24 to 54% greater than the corresponding values in the high-flow regimens (Table 6). As total weekly treatment time progressively increases (regimens D and E), increases are achieved in effective clearances over the entire solute MW spectrum. However, these increases are most pronounced for the larger solutes. A 2.22-fold difference in urea EKR is observed between regimens A and E, whereas the same comparison for inulin yields a 3.62-fold difference (Table 6). Of note, the differences for β2M are less striking due to this solute’s substantial nonrenal clearance, which comprises a significant percentage (29 to 63%) of the total clearance in all regimens.

**Effect of Rebound on EKR**

Time-averaged solute concentration is typically derived from an immediate posttreatment blood sample, leading to a certain degree of underestimation of this parameter. This results in an overestimation of EKR in an amount proportional to the difference between the immediate post-HD and equilibrated solute concentrations, an effect most pronounced for the two high-flow regimens. However, in the present study, the TAC used to determine the EKR values in Tables 4 and 5 employed equilibrated post-HD solute concentrations. In Table 7, the percent difference between EKR values derived from immediate post-HD concentrations and those based on achieved in effective clearances over the entire solute MW spectrum. However, these increases are most pronounced for the larger solutes. A 2.22-fold difference in urea EKR is observed between regimens A and E, whereas the same comparison for inulin yields a 3.62-fold difference (Table 6). Of note, the differences for β2M are less striking due to this solute’s substantial nonrenal clearance, which comprises a significant percentage (29 to 63%) of the total clearance in all regimens.

**Table 4. Small molecule TAC (mg/dl) and EKR (ml/min)**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Urea TAC</th>
<th>EKR</th>
<th>Kt/V (per week)</th>
<th>Creatinine TAC</th>
<th>EKR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>46.6</td>
<td>13.4</td>
<td>4.16</td>
<td>9.25</td>
<td>10.8</td>
</tr>
<tr>
<td>B</td>
<td>45.0</td>
<td>13.9</td>
<td>4.04</td>
<td>9.01</td>
<td>11.1</td>
</tr>
<tr>
<td>C</td>
<td>49.0</td>
<td>12.8</td>
<td>3.64</td>
<td>8.58</td>
<td>11.7</td>
</tr>
<tr>
<td>D</td>
<td>29.5</td>
<td>21.2</td>
<td>6.00</td>
<td>5.15</td>
<td>19.4</td>
</tr>
<tr>
<td>E</td>
<td>21.1</td>
<td>29.7</td>
<td>8.32</td>
<td>3.64</td>
<td>27.5</td>
</tr>
</tbody>
</table>

* TAC, time-averaged solute concentration; EKR, equivalent renal clearance.

**Table 5. Middle and large molecule TAC (mg/L) and EKR (ml/min)**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Vancomycin</th>
<th>Inulin</th>
<th>β2M</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAC</td>
<td>EKR</td>
<td>TAC</td>
<td>EKR</td>
</tr>
<tr>
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<td>30.4</td>
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<td>80.6</td>
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<td>28.6</td>
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<td>8.7</td>
<td>52.4</td>
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<tr>
<td>D</td>
<td>13.7</td>
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<td>31.7</td>
</tr>
<tr>
<td>E</td>
<td>9.7</td>
<td>20.6</td>
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* Abbreviations as in Table 4.

**Table 6. Normalized EKR values**

<table>
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<tr>
<th>Regimen</th>
<th>Urea</th>
<th>Creatinine</th>
<th>Vancomycin</th>
<th>Inulin</th>
<th>β2M</th>
</tr>
</thead>
<tbody>
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<td>A</td>
<td>1.04</td>
<td>1.03</td>
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<td>B</td>
<td>0.96</td>
<td>1.08</td>
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<td>1.80</td>
<td>2.21</td>
<td>2.57</td>
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<td>D</td>
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<td>2.55</td>
<td>3.12</td>
<td>3.62</td>
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**Table 7. Percent difference in EKR: immediate postdialysis versus equilibrated solute concentration**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Urea</th>
<th>Creatinine</th>
<th>Vancomycin</th>
<th>Inulin</th>
<th>β2M</th>
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<td>B</td>
<td>5.6</td>
<td>10.2</td>
<td>11.3</td>
<td>14.8</td>
<td>14.8</td>
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<td>3.1</td>
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</table>
equilibrated concentrations are shown for regimens A and B. (Similar data for regimen C are shown for comparative purposes.) These results suggest that use of an immediate post-treatment, rather than an equilibrated, sample results in a relatively modest (3 to 10%) overestimation of small solute EKR values but a more pronounced (11 to 16%) overestimation of EKR values for the larger solutes.

**Effect of Intercompartment Clearance on EKR and TAC: A Sensitivity Analysis**

To assess quantitatively the effect of intercompartment clearance on the kinetic parameters, TAC and EKR for urea and inulin were determined at three different $K_{IC}$ values. The results of these analyses, in which regimen A was used, are given in Tables 8 and 9. These data show that a twofold increase in urea intercompartment mass transfer rate resulted in a 6% decrease in urea TAC and 6% increase in urea EKR. However, the same twofold increase in inulin $K_{IC}$ resulted in a 18% decrease and 21% increase in inulin TAC and EKR, respectively. Furthermore, a threefold increase in inulin $K_{IC}$ produced a 24% decrease and 32% increase in inulin TAC and EKR, respectively. These data suggest that the relative effect of changes in intercompartment mass transfer on effective solute removal increases as absolute $K_{IC}$ decreases.

**Discussion**

The primary goal in developing this two-compartment HD model was to compare effective solute clearances achieved with different treatment regimens over a wide MW spectrum. The model permitted the comparison of solute clearances for regimens of varying duration, frequency, and flow rates, to those provided by a typical three-times-weekly high-flux HD regimen. The model incorporated the effects of these varying treatment parameters on solute kinetics by use of the EKR, which is a continuous-equivalent parameter accounting for the differing relationship between clearance and actual solute removal among disparate therapies (8).

One alternative regimen that has been proposed recently for use in the home HD setting consists of frequent treatments of short duration (7). The validity of the rationale for this proposed regimen, that being a more efficient utilization of the small solute depuration curves, was confirmed by our analyses. Although the total (weekly) treatment time for regimen B was approximately 3% lower than that of regimen A, predicted small solute EKR values for the former schedule were 3 to 4% higher than those of the control regimen. In addition, the model predicted that the differences in effective removal were even somewhat more pronounced for the middle molecules (vancomycin and inulin) investigated. Because dialyzer solute clearances in regimens A and B were essentially the same, regimen B can be viewed as a truncated version of regimen A. A comparison of Figure 2, a and b, demonstrates that the relatively flat (inefficient) portion of the depuration curve (for the perfused compartment) is reached earlier for inulin than for urea. Truncation at 100 min consequently has a relatively greater effect on inulin removal than on urea removal because this maneuver results in a relatively greater reduction in time spent on the flat portion of the inulin depuration curve. However, it is important to note that the predicted EKR values for regimen B are based on the assumption that treatment is administered daily with a specific volume of dialysate (i.e., 60 L) per treatment. Therefore, similar regimens administered less frequently or with a smaller volume of dialysate per treatment would produce proportionately lower EKR values for all solutes.

We also assessed the solute removal capabilities of regimens using relatively low flow rates over a long treatment duration (8 h). These regimens have also been proposed as useful for the home HD setting due to their overall solute removal capabilities and the beneficial effect of low flow rates on hemodynamic stability (5). The relative inefficiency of these regimens is demonstrated by comparing effective urea removal for regimens A and C. Although the total (weekly) treatment time of regimen C (24 h) was twice that of regimen A, the predicted urea EKR for the former schedule was actually 4% lower than that of the control schedule. For the larger (more slowly diffusing) solutes, the significantly longer total treatment time in regimen C resulted in greater effective removal by this regimen compared with that of the control regimen. This finding is consistent with the principle that as solute MW increases, diffusive solute removal increasingly becomes more time-dependent and less flow rate-dependent (40). This principle is even more clearly illustrated by comparing the relative differences between urea and inulin removal for the control regimen and the daily regimen of 8 h duration (56 h weekly treatment time).

Our modeled data demonstrate that it is possible to provide chronic HD patients with treatment schedules that enhance solute removal over a wide MW spectrum. In addition, those regimens using long treatment durations and relatively low

**Table 8. Effect of intercompartment clearance on urea kinetic parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$K_{IC}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>500</td>
</tr>
<tr>
<td>TAC (mg/dL)</td>
<td>47.5</td>
</tr>
<tr>
<td>EKR (ml/min)</td>
<td>13.2</td>
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<tr>
<td>Rebound (%)</td>
<td>19.6</td>
</tr>
</tbody>
</table>

*Units for $K_{IC}$ are ml/min. Analyses performed for regimen A.*

**Table 9. Effect of intercompartment clearance on inulin kinetic parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$K_{IC}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50</td>
</tr>
<tr>
<td>TAC (mg/L)</td>
<td>95.3</td>
</tr>
<tr>
<td>EKR (ml/min)</td>
<td>3.15</td>
</tr>
<tr>
<td>Rebound (%)</td>
<td>93.2</td>
</tr>
</tbody>
</table>

*Units for $K_{IC}$ are ml/min. Analyses performed for regimen A.*
flow rates may afford greater hemodynamic stability. These advantages over typical three-times-weekly schedules may translate into reduced morbidity and mortality in chronic HD patients. However, this hypothesis remains to be tested. In addition, the potential pitfalls of these alternative regimens require consideration. These potential drawbacks include increased anticoagulation needs, iatrogenic depletion syndromes (e.g., phosphorus, amino acids), and patient compliance issues, particularly with the high-frequency regimens. These potential risks and benefits will need to be assessed in clinical evaluations.

A secondary aim of this study was to assess intradialytic solute compartmentalization by quantifying the extent of posttreatment rebound. The realization that compartment effects must be considered for the accurate assessment of dialytic solute removal was made by numerous early investigators working in the chronic HD field (1,2,21,41). The clinical consequence of intradialytic compartmentalization is posttreatment rebound (equilibration), which has been the subject of numerous recent investigations of urea kinetics (3,13,14,25,42–44). These studies have confirmed the inability of a single-compartment model to describe adequately the kinetic behavior of urea despite this solute’s relatively fast rate of intercompartment mass transfer. These studies have also documented the decrease in effective delivered treatment dose (urea $K_t/V$) when compartment effects are considered with a two-pool model. Although most attention has focused on urea, the rebound kinetics of other solutes, including creatinine (13,14,43,44), vancomycin (11,45–47), and $\beta_2$M (9,48,49), also have recently been assessed. These latter studies have suggested that intercompartmental resistances and, consequently, intradialytic compartmentalization are greater for these larger, more slowly diffusing solutes than for urea. These studies suggest that multicompartment modeling is required for accurate estimates of HD quantification, particularly for the removal of relatively large solutes during high-efficiency therapies.

The clinical utility of the present model can be assessed by comparing our predictive data with actual (clinical) data derived from similar dialysis regimens. Specifically, the posttreatment rebound values predicted by our model for regimen A can be compared to values reported in the literature for three-times-weekly HD regimens. Although urea rebound values from previous studies have been quite variable, ranging from approximately 10 to 30%, the 16% urea rebound predicted for regimen A by our model falls squarely in the middle of this range. For creatinine, Tattersall et al. (14) reported mean post-HD rebound values of 21% for conventional HD (mean creatinine clearance, 113 ml/min) and 36% for hemodiafiltration (mean creatinine clearance, 234 ml/min). The intermediate rebound value of 31% predicted for creatinine in regimen A of our model suggests close concordance with Tattersall’s clinical data, as the creatinine clearance for regimen A (196 ml/min) was proportionally intermediate between the two clearance values from the Tattersall study. In a group of ESRD patients treated with the CT190® dialyzer, DeSoi et al. (46) reported a mean vancomycin clearance (102 ml/min) similar to that used for regimen A of the current study (117 ml/min). The mean vancomycin rebound in the DeSoi study was 38%, closely approximating the value predicted by our model (41%). In addition, Bohler et al. (45) reported a similar mean percent rebound (36%) for vancomycin in a group of patients treated with a high-flux polysulfone dialyzer. Finally, although clinical data describing the extent of clinical post-HD $\beta_2$M rebound have only been reported in preliminary form (48,49), a recently published mathematical model (9) predicted mean $\beta_2$M rebound to be 49% after high-flux HD. This value very closely approximates the regimen A value (45%) predicted by our own model. Therefore, several lines of evidence suggest that our model is capable of predicting accurately the extent of solute rebound and, by inference, effective solute removal with high-flux HD. However, validation of the model with clinical data is necessary for confirmation.

Despite the apparent clinical utility of this model, its potential deficiencies require comment. One possible problem is the manner in which in vivo solute clearances were estimated from dialyzer KoA values. KoA represents the theoretical maximal clearance for a particular solute-dialyzer combination (31) and is used to determine solute clearance under a given set of dialyzer flow rates ($Q_b$ and $Q_D$). For all solutes except $\beta_2$M, in vivo KoA values were derived from in vitro parameters, a process that may have led to errors in our estimates for in vivo dialyzer clearances. Another potential weakness of the model is related to our use of a constant intercompartment clearance value for each solute regardless of the regimen modeled. Because intercompartment clearance may be inversely related to extracorporeal blood flow rate, intercompartment clearance could have been relatively low for the high efficiency regimens (A and B) and relatively high for the low efficiency regimens (C, D, and E). However, there is no definitive proof of this in the literature. A final potential limitation of the model is the assumption that solute generation and nonrenal clearance applied only to the perfused compartment. However, the same assumption has been made in the vast majority of prior modeling studies (1,2,9,18,19,21,24,26,27). In addition, an early theoretical study (41) showed that predicted therapy requirements to achieve defined target solute concentrations were not different when solute generation was applied to either the intracellular or extracellular compartment.

In summary, we have developed a model allowing quantitative comparisons of effective solute removal by disparate chronic HD schedules. The model incorporates the effect of compartmentalization for uremic surrogate solutes over a wide MW spectrum. This broad solute MW range is important in light of recent data demonstrating a positive correlation between survival and both small solute clearance (50) and middle molecule clearance (51) in chronic HD patients. This tool should be useful as alternative HD regimens designed to improve clinical outcomes are investigated.

Acknowledgments
The authors thank Dr. Thomas Depner for his helpful comments in the preparation of this manuscript.
Appendix 1

\( F \): Frequency (per week)

\( T \): Time (min)

\( Q_B \): Blood flow rate (ml/min)

\( Q_D \): Dialysate flow rate (ml/min)

\( U \): Urea

\( Cr \): Creatinine

\( V \): Vancomycin

\( I \): Insulin

\( \beta 2M \): \( \beta 2 \)-microglobulin

\( G \): Solute generation rate (mg/min)

\( MM \): Middle molecule

\( EKR \): Equivalent renal clearance (ml/min)

\( K_{IC} \): Intercompartment clearance (ml/min)

\( K_{NR} \): Nonrenal clearance (ml/min)

\( K_{DP} \): Diallyzer clearance (ml/min)

\( V_D \): Volume of distribution (L)

\( TBW \): Total body water (L)

\( V_P \): Perfused compartment volume (L)

\( V_{NP} \): Nonperfused compartment volume (L)

\( K_A \): Diallyzer permeability-area product (ml/min)

\( TAC \): Time-averaged solute concentration (mg/dL or mg/L)

\( T_D \): Dialysis (treatment) time (min)

\( T_R \): Rebound time (min)

\( T_{ID} \): Interdialytic time (min)

\( C_P \): Predialysis solute concentration (mg/dL or mg/L)

\( C_T \): Immediate postdialysis solute concentration (mg/dL or mg/L)

\( C_{EQ} \): Equilibrated postdialysis solute concentration (mg/dL or mg/L)

Appendix 2

Mass Balance Equations

\[ \frac{d(X_P)}{dt} = G - K_{IC}(C_P - C_{NP}) - K_D \cdot \text{Ind} \cdot C_P - K_{NR} \cdot C_P \]

\[ d(X_{NP}) = K_{IC}(C_P - C_{NP}) \]

\[ dV_D/dt = \alpha(1 - \text{Ind}) - \frac{Q_{UF}}{\text{Ind}} \]

\[ d(V_P)/dt = \Phi_P(1 - \text{Ind}) - \frac{Q_{UF}}{\text{Ind}} \]

\[ d(V_{NP})/dt = \Phi_{NP}(\alpha(1 - \text{Ind}) - \frac{Q_{UF}}{\text{Ind}}) \]

Nomenclature (in addition to that listed in Appendix 1)

\( t \): Time at any point

\( T \): Total cycle time (\( T_D + T_{ID} \))

\( \text{Ind} \): Indicator variable such that \( \text{Ind} = 1 \) if \( 0 \leq t \leq T_D \) and \( \text{Ind} = 0 \) if \( T_D < t < T \)

\( C_P \): Solute concentration in perfused compartment (mg/dL or mg/L)

\( C_{NP} \): Solute concentration in nonperfused compartment (mg/dL or mg/L)

\( Q_{UF} \): Net intradialytic ultrafiltration rate (ml/min)

\( \Phi_P \): Constant ultrafiltration ratio for perfused compartment

\( \Phi_{NP} \): Constant ultrafiltration ratio for nonperfused compartment

\( X_P \): Mass of solute in perfused compartment (mg)

\( X_{NP} \): Mass of solute in nonperfused compartment (mg)

\( \alpha \): Rate of fluid intake (ml/min)

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