Kinetics and dosing predictions for daily haemofiltration

John K. Leypoldt¹, Bertrand L. Jaber², Michael J. Lysaght³, James T. McCarthy⁴ and John Moran⁵

¹Research Service, Salt Lake City VA Health Care System and Departments of Internal Medicine and Bioengineering, University of Utah, Salt Lake City, UT, ²Division of Nephrology, New England Medical Center, Boston, MA, ³Department of Biomedical Engineering, Brown University, Providence, RI, ⁴Division of Nephrology, Mayo Clinic, Rochester, MN and ⁵Vasca, Tewksbury, MA, USA

Abstract

Background. Thrice-weekly haemofiltration affords excellent outcome when it is used to treat chronic renal failure patients. Daily haemofiltration (DHF) has recently been proposed as a more intensive therapy option, but the total ultrafiltration or exchange volume (replacement volume plus net ultrafiltration volume) requirements for adequate solute clearances during this novel therapy are unknown.

Methods. We calculated theoretical solute kinetic profiles during six times per week DHF for comparison with those during thrice-weekly haemodialysis using a high-flux dialyser (HFHD) or during continuous ambulatory peritoneal dialysis (CAPD). HFHD and CAPD were chosen for comparison because KDQI guidelines have defined adequate treatment doses for these therapies. Steady-state concentrations were calculated using a two-compartment model of an anuric patient with 35 l of total body water for five solutes: urea, creatinine, vitamin B₁₂, inulin and β₂-microglobulin. Solute distribution volumes and generation rates were taken from the literature, and excess fluid (1 l/day) was assumed to accumulate in and be removed from the extracellular fluid compartment. Theoretical predictions of solute clearance were compared for a 15-l exchange volume/session during DHF, urea Kt/V of 3.6/week during HFHD and urea Kt/V of 2.0/week during CAPD as solute-specific values of the equivalent renal clearance (EKR) and standard Kt/V recently defined by Gotch.

Additional comparisons of solute clearances were performed between DHF and other daily therapies including six times per week short daily haemodialysis (SDHD) and six times per week nocturnal haemodialysis (NHD).

Results. The calculated results predict that: (i) urea clearance during DHF with an exchange volume of 90 l/week (6 × 15 l) is equivalent to those during HFHD and CAPD based on urea stdKt/V; and (ii) middle molecule clearances during DHF exceed those achieved during HFHD and CAPD based on either EKR or stdKt/V. As expected, DHF therapy was inferior regarding the clearance of urea and other small solutes to SDHD and NHD; however, DHF therapy was superior to SDHD regarding the clearance of larger middle molecules, approaching the clearances achieved by NHD.

Conclusions. We predict that an exchange volume of ~40% of total body water (15/35 l = 43%) per session will provide adequate clearance of small solutes and substantial clearance of middle molecules during six times per week DHF therapy. These theoretical predictions require clinical validation.

Keywords: daily; dose; haemofiltration; kinetics; Kt/V; urea

Introduction

Haemofiltration was developed in the middle 1960s as an alternative to haemodialysis and peritoneal dialysis that would provide solute clearance characteristics more like those of the native kidney [1]. This modality is performed using highly permeable membranes and makes use of convective solute removal; these two characteristics of haemofiltration are also those employed by the native kidney. During haemofiltration, solutes from urea to middle molecules are cleared at the same rate, allowing substantial removal of middle molecules. Patient outcome when using chronic three times per week haemofiltration therapy has been reported to be excellent among many centres throughout the world [2,3].

Despite the advantage of enhanced clearance of middle molecules, haemofiltration is not widely employed to treat patients with chronic renal failure,
Subjects and methods

Solute kinetics were simulated theoretically using a variable-volume, two-compartment mathematical model for three different treatment modalities, DHF, haemodialysis using a HFHD and CAPD, to calculate an exchange volume for achieving adequate solute clearances during DHF therapy. Additional, but more limited, comparison was also performed between DHF and other daily therapies including short daily haemodialysis (SDHD) and nocturnal haemodialysis (NHD). Steady-state solute concentration profiles were simulated for five uraemic surrogate solutes with a broad molecular weight spectrum (Table 1). No binding to plasma proteins was assumed to occur for any solute.

The mathematical model allowed for partition of solutes into two different compartments (Figure 1) [7]. The total volume of distribution for each solute was partitioned into a compartment from which solute was directly removed (termed the perfused compartment) and a compartment from which solute removal was only allowed after transfer into the perfused compartment (termed the non-perfused compartment). These volumes of distribution were allowed to vary with time due to interdialytic fluid intake and intradialytic fluid removal. The total volume of distribution for urea, creatinine and vitamin B12 was assumed to be equal to the volume of total body water. Of this total, one-third was assumed to be confined within the perfused (extracellular) compartment and two-thirds within the non-perfused (intracellular) compartment. For inulin and $\beta_2$-Microglobulin, the total volume of distribution was assumed to be the extracellular compartment, with intravascular fluids (one-quarter of extracellular volume) and interstitial fluids (three-quarters of extracellular volume) as the perfused and non-perfused compartments, respectively. All computer simulations were performed for an anephric patient with a dry (post-dialysis) weight of 70 kg, and total body water was assumed to be 50% of dry weight. This latter assumption was a compromise between those estimated using anthropometric equations and the lower values estimated from urea kinetics during chronic haemodialysis therapy [10]. All fluid gained by and removed from the patient was assumed to occur with the extracellular compartment; the relative amounts removed from the intravascular and interstitial fluids were assumed to be proportional to the compartment volumes (one-quarter and three-quarters, respectively).

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Table 1. Solute characteristics

<table>
<thead>
<tr>
<th>Solute</th>
<th>Molecular weight</th>
<th>$G^u$ (mg/min)</th>
<th>$K_{IC}^b$ (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>60</td>
<td>6.25</td>
<td>600</td>
</tr>
<tr>
<td>Creatinine</td>
<td>113</td>
<td>1.0</td>
<td>275</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>1355</td>
<td>0.2</td>
<td>125</td>
</tr>
<tr>
<td>Inulin</td>
<td>5200</td>
<td>0.3</td>
<td>90</td>
</tr>
<tr>
<td>$\beta_2$-Microglobulin</td>
<td>11 800</td>
<td>0.17</td>
<td>40</td>
</tr>
</tbody>
</table>

$^aG$, solute generation rate.

$^bK_{IC}$, intercompartmental transfer constant or clearance.

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Fig. 1. Schematic description of the mechanisms governing solute transport in the two-compartment model. The volume of distribution for each solute was compartmentalized into perfused and non-perfused compartment volumes ($V_p$ and $V_{np}$, respectively). The plasma water solute concentrations in these compartments are labelled $C_p$ and $C_{np}$, respectively. Solutes are generated or removed only from the perfused compartment by a constant solute generation rate ($G$), a non-renal clearance ($K_{NR}$) or solute removal during treatment ($J_s$). Solute transport between compartments is governed by the intercompartmental transfer coefficient ($K_{IC}$).
Dosing predictions for daily haemofiltration

Solute generation was assumed to occur only within the perfused compartment. Endogenous solute generation was assumed to be constant for urea, creatinine and $\beta_2$-microglobulin, with generation rates identical to the values assumed by Clark et al. [7] (Table 1). Vitamin B$_{12}$ and insulin are not naturally generated within the body; nevertheless, it was assumed that these solutes were generated at constant rates to predict reasonable concentrations for calculating solute dose measures, as described previously [7]. The absolute magnitudes of the assumed solute generation rates are rather unimportant in this study as calculated solute clearances are relatively independent of the assumed generation rates.

Solute transfer between the compartments was assumed to be proportional to the solute concentration difference; the proportionality constant was defined as the intercompartmental transfer constant or clearance $K_{IC}$. The values of $K_{IC}$ for each solute were assumed to be identical to those reported previously (Table 1), and these values were shown previously to predict post-dialysis rebound of solutes similar to those observed experimentally [7].

The rate of fluid removal during DHF, HFHD, SDHD and NHD was assumed constant throughout the treatment. During DHF, the rate of fluid removal was assumed to be equal to the ultrafiltration rate minus the infusion rate of replacement fluid. During HFHD, SDHD and NHD, the rate of fluid removal was assumed to be equal to the ultrafiltration rate. During CAPD, the rate of fluid removal was dependent on the glucose concentration in the dialysate and was assumed to be equal to the time-dependent ultrafiltration rate predicted by the model of Pyle [11] (see Appendix). For each treatment modality, weekly fluid removal was matched to weekly fluid accumulation so that overall patient volume was at steady state. Unless stated otherwise, the rate of fluid intake or accumulation was assumed to be constant and equal to 1 l/day.

Solute removal from the body was evaluated differently for each treatment modality; the details of these relationships are described in the Appendix. During DHF, six identical 2.5-h treatments per week were simulated; 1 day was without any treatment. Solute clearance during DHF therapy was assumed to be proportional to the ultrafiltration rate; the convective permeability factor was the solute sieving coefficient. The solute sieving coefficients during DHF for most calculations in this study were based on reported in vitro measurements conducted with either bovine or human plasma with a protein concentration of 6 mg/dl [12,13]. The assumed values are shown in Table 2. During HFHD, three 3-h treatments per week were simulated on a traditional Monday/Wednesday/Friday schedule. Solute clearances during HFHD were calculated assuming the use of a HFHD, a blood flow rate of 340 ml/min and a dialysate flow rate of 500 ml/min in order to achieve a single pool urea Kt/V of 1.2/treatment. The dialyser mass transfer-area coefficients for each solute in this study were assumed to be ~20% higher than those assumed by Clark et al. [7] and are shown in Table 2. These values were chosen as a compromise between those assumed by Clark et al. [7] and in vivo mass transfer-area coefficients for urea reported recently for HFHD (T.A. Depner, T. Green, J.T. Daugirdas et al., manuscript submitted for publication). Dialyser solute clearances during HFHD were also adjusted for ultrafiltration (see Appendix). SDHD therapy consisted of six 2.5-h treatments, under identical conditions to those assumed during HFHD, and NHD therapy consisted of six 8-h treatments assuming a HFHD with mass transfer-area coefficients 60% of those described in Table 2, a blood flow rate of 250 ml/min and a dialysate flow rate of 100 ml/min, conditions reflective of the use of small surface area HFHD and flow rates as reported by Pierratos et al. [14]. Solute clearances during SDHD and NHD were calculated in a similar way to those during HFHD. Five 2-l exchanges per day were simulated during CAPD. Solute transport across the peritoneal membrane was calculated accounting for both diffusive and convective transport (see Appendix).

Solute transport rates by diffusion and convection were assumed to be related to the permeability-area product (PA) and the solute reflection coefficient ($\sigma$), respectively, for the peritoneal membrane; the assumed values of these parameters are listed in Table 2. Non-renal clearance was assumed to be zero, except for $\beta_2$-microglobulin where it was assumed to be 3 ml/min [15].

Steady-state solute concentration profiles for each solute were computed by iterative solution of the governing equations (see Appendix) over a 10-week interval. The governing equations were solved by using a variable time-step, fourth-fifth order Runge–Kutta algorithm [16]. From the steady-state concentration profiles, several additional parameters were calculated. The time-averaged concentration (TAC) was obtained for each solute/modality combination as a time- and volume-weighted average of the intradialytic and interdialytic concentrations, assuming these concentrations were linear during the intradialytic, immediate post-dialysis rebound and interdialytic periods as described elsewhere [7]. The immediate post-dialysis rebound period was assumed to be 1 h for urea, creatinine and vitamin B$_{12}$, and 4 h for insulin and $\beta_2$-microglobulin. TACs for the intradialytic and interdialytic solute concentration profiles were first calculated for the perfused and non-perfused compartments separately; then, the whole body TAC was calculated by averaging the individual compartment TAC values, weighted for the compartment volumes. With the assumed solute generation rate ($G$) and calculated whole body TAC values known, the EKR was then calculated as described previously [7,8]

$$\text{EKR} = \frac{G}{\text{TAC}}.$$  

The mean pre-treatment concentration (MPC) was calculated by averaging the pre-treatment concentrations in the perfused compartment. The stdKt/V for each solute was then calculated by the following equation

$$\text{stdKt}/\text{V} = G \times t/\text{MPC}/V$$  

where $t$ and $V$ denote the total weekly time and volume of distribution for the solute of interest, respectively [9].

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Table 2. Solute removal characteristics during DHF, HFHD and CAPD

<table>
<thead>
<tr>
<th>Solute</th>
<th>$S^a$</th>
<th>In vivo $K_{A}$ (ml/min)$^b$</th>
<th>PA (ml/min)$^c$</th>
<th>1 -$\sigma^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>1.0</td>
<td>600</td>
<td>21</td>
<td>0.6</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.0</td>
<td>425</td>
<td>11</td>
<td>0.55</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>1.0</td>
<td>181</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>Insulin</td>
<td>1.0</td>
<td>98</td>
<td>2</td>
<td>0.4</td>
</tr>
<tr>
<td>$\beta_2$-Microglobulin</td>
<td>0.6</td>
<td>39</td>
<td>1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

$^a$ $S$, solute sieving coefficient for haemofiltration membranes [12,13].

$^b$ $K_{A}$, mass transfer-area coefficient for HFHD (~20% higher than previously assumed by Clark et al. [7]).

$^c$ PA, permeability-area for the peritoneal membrane [11,23,24].

$^d$ $\sigma$, solute reflection coefficient for the peritoneal membrane [11].
Results

Solute concentration profiles and dose measures were first calculated for 12, 15 and 18 l of exchange volume during DHF. The solute dose measures (EKR and stdKt/V) increased regularly with increasing exchange volume, as expected (Table 3). The calculated results described below were calculated based on 15 l of exchange volume for each DHF treatment session.

The effect of treatment time (between 2 and 3 h) during DHF at a constant exchange volume of 15 l on the calculated solute dose measures was small (<3%) for small solutes (i.e. urea and creatinine, Table 4). The relative importance of treatment time is larger for middle molecules (i.e. vitamin B12, inulin and β2-microglobulin), most probably because post-dialysis rebound is more substantial for these solutes [7]. These calculations show that the dose of DHF therapy for small solutes, but not for middle molecules, is largely determined by exchange volume and less influenced by treatment time.

Figure 2 shows steady-state concentration profiles in the perfused (extracellular) compartment for blood urea nitrogen during DHF, HFHD and CAPD. These calculated profiles show that the MPCs of blood urea nitrogen are similar for these different modalities: DHF using 15 l of exchange volume per session, HFHD for three sessions per week at single pool Kt/V of 1.2 per session, and CAPD using five, 2-l dwells/day.

Calculated values of TAC and MPCs for the five different solutes during DHF, HFHD and CAPD are shown in Figures 3 and 4, respectively. The magnitude of these concentrations is solute specific; nevertheless, the comparisons among DHF, HFHD and CAPD are instructive. TAC values are lower than MPCs for each solute as expected; they are approximately equal during CAPD and most disparate during HFHD. TAC values are lowest during HFHD for small solutes (urea and creatinine), but lowest during DHF of these concentrations.

![Fig. 2. Example steady-state concentration profiles for blood urea nitrogen during a week for treatment by DHF (thin solid line), CAPD (thick solid line) and haemodialysis using HFHD (dashed line).](image-url)

![Fig. 3. Calculated values of the whole body TAC for urea (U), creatinine (C), vitamin B12 (B12), inulin (I) and β2-microglobulin (Beta2M) during DHF (white bars), high-flux haemodialysis (black bars) and CAPD (striped bars). The concentrations for urea were divided by five. The units are reported in mg/dl for each solute.](image-url)

![Fig. 4. Calculated values of the MPC for urea (U), creatinine (C), vitamin B12 (B12), inulin (I) and β2-microglobulin (Beta2M) during DHF (white bars), high-flux haemodialysis (black bars) and CAPD (striped bars). The concentrations for urea were divided by five. The units are reported in mg/dl for each solute.](image-url)

**Table 3.** Calculated dose measures during DHF when using 12, 15 and 18 l of total ultrafiltration or exchange volume for a patient with 35 l of total body water

<table>
<thead>
<tr>
<th>Solute</th>
<th>EKR (ml/min)</th>
<th>stdKt/V</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 l</td>
<td>15 l</td>
</tr>
<tr>
<td>Urea</td>
<td>6.79</td>
<td>8.33</td>
</tr>
<tr>
<td>Creatinine</td>
<td>6.54</td>
<td>7.95</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>6.22</td>
<td>7.46</td>
</tr>
<tr>
<td>Inulin</td>
<td>4.53</td>
<td>5.16</td>
</tr>
<tr>
<td>β2-Microglobulin</td>
<td>5.82</td>
<td>6.22</td>
</tr>
</tbody>
</table>

**Table 4.** Calculated dose measures during DHF when using 15 l of total ultrafiltration or exchange volume for different treatment (Tx) times for a patient with 35 l of total body water

<table>
<thead>
<tr>
<th>Solute</th>
<th>EKR (ml/min)</th>
<th>stdKt/V</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 h</td>
<td>2.5 h</td>
</tr>
<tr>
<td>Urea</td>
<td>8.23</td>
<td>8.33</td>
</tr>
<tr>
<td>Creatinine</td>
<td>7.78</td>
<td>7.95</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>7.29</td>
<td>7.46</td>
</tr>
<tr>
<td>Inulin</td>
<td>4.81</td>
<td>5.16</td>
</tr>
<tr>
<td>β2-Microglobulin</td>
<td>6.05</td>
<td>6.22</td>
</tr>
</tbody>
</table>
for middle molecules (vitamin B₁₂, inulin and β₂-microglobulin). The relative impact of treatment by DHF is more substantial on TAC for middle molecules. MPC values are very similar for urea among these modalities, but lowest during DHF for all other solutes.

Calculated values of EKR and stdKt/V are shown in Figures 5 and 6, respectively. EKR values were highest during HFHD for small solutes (urea and creatinine) but highest during DHF for molecules with higher molecular weight. Values of stdKt/V were similar for urea among these modalities, but highest during DHF for all other solutes.

It should be emphasized that the advantage of DHF for clearing large molecules is dependent on the sieving properties of the membrane. If, for example, the sieving coefficients for vitamin B₁₂, inulin and β₂-microglobulin were assumed to be one-half of the values shown in Table 2, the EKR and stdKt/V values would be reduced to 4.13 ml/min and 1.10 for vitamin B₁₂, 3.29 ml/min and 2.78 for inulin, and 5.03 ml/min and 4.58 for β₂-microglobulin. Comparison of these values with those plotted in Figures 5 and 6 shows that the advantage of DHF for clearing middle molecules will be significantly compromised if membranes without high sieving coefficients are used.

All of the above results were calculated assuming a daily fluid intake of 1 l. Table 5 shows the effect of fluid intake on calculated dose measures (EKR and stdKt/V) for urea when the total ultrafiltration or exchange volume was 15 l/day. These calculated results show that at a fixed exchange volume, increases in daily fluid intake result in higher EKR and stdKt/V values for urea due to the dilution of solutes by fluid intake. Note also that the replacement fluid volume required to achieve a given exchange volume decreases with increasing daily fluid intake.

Comparisons of solute dose measures (EKR and stdKt/V) between DHF, SDHD and NHD are shown in Figures 7 and 8, respectively. Not surprisingly, SDHD and NHD lead to substantially higher small solute doses than during HFHD due to increased frequency and longer total weekly time on therapy. As a result, SDHD and NHD are superior to DHF in clearing small solutes; however, DHF remains superior to SDHD for clearing larger middle molecules irrespective of whether EKR or stdKt/V is used as the dose measure. Clearances of middle molecules during DHF therapy approach those achieved during NHD.

### Discussion

The adequacy of different treatment modalities for end-stage renal disease patients has long been a topic of debate. The results presented here suggest that DHF provides a competitive alternative to longer and more frequent treatments, such as SDHD and NHD, in clearing solutes.

### Table 5

<table>
<thead>
<tr>
<th>Fluid intake (l/day)</th>
<th>Replacement fluid volume (l)</th>
<th>EKR (ml/min)</th>
<th>stdKt/V</th>
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<tr>
<td>0</td>
<td>15.0</td>
<td>8.22</td>
<td>2.01</td>
</tr>
<tr>
<td>0.5</td>
<td>14.5</td>
<td>8.28</td>
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</tr>
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<td>1.0</td>
<td>14.0</td>
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<td>2.07</td>
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<td>1.5</td>
<td>13.5</td>
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</tr>
<tr>
<td>2.0</td>
<td>13.0</td>
<td>8.41</td>
<td>2.12</td>
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"Fig. 5. Calculated values of EKR for urea (U), creatinine (C), vitamin B₁₂ (B₁₂), inulin (I) and β₂-microglobulin (Beta2M) during DHF (white bars), high-flux haemodialysis (black bars) and CAPD (striped bars). The units are reported in ml/min for each solute. The values above each bar denote the per cent increase (+) or decrease (−) between that during the respective therapy and DHF."

"Fig. 6. Calculated values of the stdKt/V for urea (U), creatinine (C), vitamin B₁₂ (B₁₂), inulin (I) and β₂-microglobulin (Beta2M) during DHF (white bars), high-flux haemodialysis (black bars) and CAPD (striped bars). The units are reported in ml/min for each solute. The values above each bar denote the per cent increase (+) or decrease (−) between that during the respective therapy and DHF."

"Fig. 7. Calculated values of EKR for urea (U), creatinine (C), vitamin B₁₂ (B₁₂), inulin (I) and β₂-microglobulin (Beta2M) during DHF (white bars), SDHF (black bars) and NHD (striped bars). The units are reported in ml/min for each solute. The values above each bar denote the per cent increase (+) or decrease (−) between that during the respective therapy and DHF."
of debate, and several studies continue to explore the optimal dose of therapy for conventional three times per week haemodialysis and continuous peritoneal dialysis. Currently, however, K/DOQI has established generally accepted minimum dosing guidelines for both haemodialysis [17] and peritoneal dialysis [18]. Dosing guidelines for these two therapies are expressed using an indexed clearance of urea, or urea Kt/V. The dosing guidelines suggested by K/DOQI for haemodialysis and peritoneal dialysis are quite different from each other: a weekly urea Kt/V target of 3.6 (3 \times 1.2) for conventional haemodialysis and a weekly urea Kt/V target of 2.0 for CAPD. Nevertheless, these dosing guidelines represent the empirical judgment of the nephrology community based on years of experience with these therapies.

Two different approaches for evaluating the effect of treatment modality on dialysis dose and adequacy are those based on controlling either the time-averaged or the MPCs of urea, instead of urea Kt/V. Casino and Lopez [8] proposed that an adequate dose of dialysis can be assessed using the EKR, and Clark et al. [7] have shown that this parameter, corrected for solute rebound post-dialysis, can be used to evaluate the dose for more frequent or intense haemodialysis therapies. As discussed above, EKR is equivalent between therapies when time-averaged solute concentrations are equal; however, equivalent patient outcomes during haemodialysis and peritoneal dialysis are not achieved at equal values of Kt/V for urea. Alternatively, Gotch [9] has recently focused on controlling the MPC of urea for assessing the dose of renal replacement therapies. Control of the MPC of urea provides the foundation for Gotch’s hypothesis, which proposes that stdKt/V for urea is the best dose measure for comparing treatment modalities and regimens different from thrice-weekly haemodialysis, because this hypothesis supports the relative therapeutic equivalence of CAPD and conventional haemodialysis [9].

The concepts of EKR and stdKt/V are general and not limited to just urea. For example, Clark et al. [7] computed theoretical EKR values for five solutes of differing molecular weight and used this parameter to evaluate the relative efficiencies of different haemodialysis regimens to remove these solutes. In addition, Gotch has recently suggested that the stdKt/V concept should be generalized to other solutes [19]. The current study represents an attempt to compute theoretical values of stdKt/V for solutes other than urea to compare solute clearances for different modalities.

Whether based on calculated values of either EKR or stdKt/V, our comparisons between DHF, HFHD and CAPD, in terms of solute clearance (especially for middle molecules), are rather robust. Our calculated results show that EKR values for small solutes, urea and creatinine, are higher during HFHD than during DHF and CAPD, but the largest EKR values for the middle molecules were calculated during DHF (Figure 5). This dose measure suggests that HFHD is superior to DHF and CAPD in clearing small solutes but DHF is superior to both HFHD and CAPD in clearing middle molecules, including low molecular weight proteins. Our calculated results for stdKt/V show that DHF, HFHD and CAPD provide approximately equivalent weekly clearances for small solutes such as urea, but DHF is superior to HFHD and CAPD in clearing middle molecules (Figure 6). Therefore, use of either generalized dose measure shows that clearance of large molecular weight solutes during DHF will be superior to those during both HFHD and CAPD.

Exploration of new therapy modalities has recently received considerable attention; the clinical advantages of more frequent haemodialysis treatments for chronic renal failure patients have recently been reviewed [20]. Several studies have suggested that increasing the frequency and intensity of therapy improves blood pressure control, improves nutritional status and decreases complications requiring hospitalization in chronic haemodialysis patients [20]. Some of these improvements are probably due to the more continuous nature of the therapy, while others are also potentially due to the increased dose, both in terms of small solute and middle molecule clearances. The ability to assess the relative importance of small solute and middle molecule clearances for improving haemodialysis patient outcome is controversial. As a result, dosing guidelines for these therapies are not yet universally defined. Our comparison of solute clearances between DHF and other daily therapies (Figures 7 and 8) illustrates that diffusion-based (haemodialysis) therapies (SDHD and NHD) provide higher clearances of small solutes. DHF therapy, however, clears more of the larger middle molecules than SDHD; the clearances of middle molecules with DHF approach those achieved by NHD, the therapy that provides the highest clearances for both small solute and middle molecules to date.

DHF also has the potential to improve clinical outcomes vs conventional therapies for chronic renal failure patients. Again, some of the improvements may arise from the daily, more continuous nature of the therapy (as above), but historical experience with chronic haemofiltration therapy suggests that other benefits may arise from the broader, more physiologic clearance profile, which more closely mimics the natural renal glomerulus. Because of these
significant differences in the therapy provided, establishing equivalent dosing is made even more complex. The current effort is a first attempt to predict dosing requirements for DHF using generally accepted solute dose measures. Assuming that an stdKt/V for urea of 2.0 defines adequate therapy, this study predicts that the dose of DHF is an exchange volume of ~40% of total body water (15/35 1 = 43%) six times per week. It should be noted that this prediction might be conservative as such a dose of therapy will also provide the additional benefit of enhanced clearances of middle molecules. On the other hand, there is substantial room for improving outcomes for end-stage renal disease patients; thus, it is likely that solute clearance targets may be higher for all renal replacement therapies in the near future. Clearly, further refinement of this and more extensive predictions will require empirical clinical comparisons with treatment outcomes.

Several limitations of this study should be noted. First, we have assumed that no protein binding of solutes occurs. This is likely to be a good assumption for some small solutes, such as urea and creatinine, but may not be realistic for other molecules of interest, especially vitamin B12. Secondly, calculated values of EKR for urea in this study do not achieve the minimum of 11 ml/min as originally proposed by Casino and Lopez [8]. It should be pointed out, however, that Casino and Lopez calculated EKR values assuming that the distribution volume of urea was a single body pool and therefore did not account for post-dialysis urea rebound. Thirdly, the current theoretical predictions assumed a fluid intake of 1 l/day, a value that may be low for some end-stage renal disease patients. Our additional calculations (Table 5) show, however, that the exchange volume requirements to achieve a given dose of urea removal actually decrease with increasing fluid intake. Fourthly, the ultrafiltration flow rate required to achieve 15 l of ultrafiltration in 2.5 h of 100 ml/min will require high blood flow rates, approaching 500 ml/min. Therefore, it may be necessary to lengthen treatment times for patients with large body weight and those unable to achieve high blood flows without access recirculation. Any lengthening of treatment times at the same exchange volume will only lead to enhanced middle molecule clearances. Previous studies by Canaud and colleagues [21] have reported average ultrafiltration rates of over 125 ml/min during 3-h treatments of daily post-dilution haemofiltration, suggesting that the current predictions are reasonable. Lastly, our theoretical predictions are limited by the accuracy of the assumed transport parameters. For example, differences in peritoneal membrane transport characteristics among patients may yield clinical results different from those predicted here. Similar discrepancies between the current theoretical predictions and observed clinical results are also possible for haemofiltration and haemodialysis treatments if membranes with unique transport properties are employed.

We conclude that solute clearances during DHF with an exchange volume of ~40% of total body water six times per week are theoretically equivalent to, or better than, those during HFHD and CAPD (based on stdKt/V). These calculations therefore suggest that DHF is practical in today’s environment, given the approximate time required to perform the daily treatment and the similarity in fluid requirements to current therapy modalities (CAPD and automated forms of peritoneal dialysis). These theoretical predictions require clinical validation.

Acknowledgements. This work was supported by the Department of Veterans Affairs, Dialysis Research Foundation (Ogden, UT) and NxStage Medical (Lawrence, MA).

Conflict of interest statement. J.K.L. and B.L.J. are currently conducting research sponsored by NxStage medical. J.M. is a member of the Scientific Advisory Board for NxStage medical. M.J.L. and J.T.M. have declared no conflicts of interest.

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Appendix

The equations governing solute concentrations in the perfused and non-perfused compartments are based on mass balances within each compartment as described previously [7]:

\[
\frac{d(C_p V_p)}{dt} = G - K_{IC}(C_p - C_{np}) - J_s - K_{NR} * C_p \tag{A1}
\]

\[
\frac{d(C_{np} V_{np})}{dt} = K_{IC}(C_p - C_{np}) \tag{A2}
\]

\[
V_p / dt = -J_s \tag{A3}
\]

\[
V_{np} / dt = 0 \tag{A4}
\]

where \( J_s \) and \( J_v \) denote solute and volume removal rates, respectively. In these equations, \( C_p \) and \( C_{np} \) denote the solute concentrations in the water phase only. \( J_s \) was set equal to zero during intertreatment intervals for DHF, HFHD and daily haemodialysis therapies (SDHD and NHD). The above equations describe changes in intercompartmental volumes only for urea, creatinine and vitamin B12. When considering inulin and \( \beta_2 \)-microglobulin, changes in volume for the perfused and non-perfused compartments were assumed as follows:

\[
\frac{dV_p}{dt} = -J_v / 4 \tag{A5}
\]

\[
\frac{dV_{np}}{dt} = -3 * J_v / 4 \tag{A6}
\]

Solute and volume removal rates were dependent on the treatment modality. During DHF, the solute removal rate was described by the following equation:

\[
J_s = Q_t * S * C_p \tag{A7}
\]

where \( Q_t \) denotes the ultrafiltration rate. The volume removal rate \( (J_v) \) was assumed to be equal to the ultrafiltration rate minus the infusion rate of replacement fluid. During HFHD, the solute removal rate was described by the following equation:

\[
J_s = (K_d + 0.4 * Q_t) C_p \tag{A8}
\]

where \( K_d \) denotes solute clearance in the absence of ultrafiltration, which was calculated using standard formulae [7] from the blood water and dialysate flow rates and the in vivo \( K_a \) values reported in Table 2. The second term in the parentheses denotes an approximate correction factor for increased solute removal due to ultrafiltration that has been shown to be approximately valid for both urea and \( \beta_2 \)-microglobulin [22]. The methods for calculating solute removal during SDHD and NHD were identical to those during HFHD.

Solute removal rates during CAPD were calculated from the following equation [11]:

\[
J_s = PA(C_p - C_d) + (1 - \sigma) * Q_t * C_p \tag{A9}
\]

where \( PA \) and \( 1 - \sigma \) are reported in Table 2. During CAPD, the change in the dialysate concentration with time is governed by the following equation

\[
\frac{d(C_d V_d)}{dt} = J_s - Q_L * C_d \tag{A10}
\]

where \( V_d \) denotes the volume of dialysis solution within the peritoneal cavity and \( Q_L \) denotes the rate of fluid absorption from the peritoneal cavity. The transperitoneal ultrafiltration rate was assumed to be time dependent as described previously [11]. The coefficients of the exponential equation describing transperitoneal ultrafiltration were dependent on the assumed glucose concentration of the freshly infused dialysis solution for each exchange. The fluid absorption rate from the peritoneal cavity was assumed to be the rate defining the decrease in peritoneal volume after osmotic equilibration between plasma and the dialysis solution [11], and residual volume between exchanges was assumed to be zero. CAPD was assumed to consist of five exchanges per day, four for 4 h and one for 8 h. The short dwells were assumed to use 1.5% glucose-containing dialysate and the long dwell was assumed to use 4.25% glucose-containing dialysate.