Effect of treatment spacing and frequency on three measures of equivalent clearance, including standard Kt/V

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Abstract

Background. We examined the sensitivity of three different equivalent clearances to the spacing of haemodialysis treatments as well as to frequency. One would expect that a well-spaced schedule would be beneficial, and an optimal clearance measure should reflect this.

Methods. Using a variable volume two-pool urea kinetic model, we derived clearances based on G [urea nitrogen (UN) generation rate] divided by time-averaged UN (G/TAC), mean predialysis UN (G/meanpre or ‘standard’ Kt/V) or peak UN (G/peak) when identical dialysis treatments were given on a poorly spaced (Monday—Tuesday—Wednesday) versus a well-spaced (Monday—Wednesday—Friday) schedule. We also calculated the ‘gain’ in each clearance when well-spaced treatments were given six versus three times a week. Modelling parameters were diffusive dialyser clearance = 283 ml/min, session length = 210 min (105 min for 6/week), G = 7 mg/min, V = 35 l and weight gain = 10 l/week.

Results. The ‘standard’ Kt/V (G/meanpre) was the same with the poorly spaced (Monday—Tuesday—Wednesday) and well-spaced (Monday—Wednesday—Friday) schedules. In contrast, the G/TAC- and G/peak-based clearances were higher with the well-spaced schedule (+20% and +37%, respectively).

When total treatment time was held constant at 630 min/week, the gain of moving from three to six treatments per week was lower with G/TAC (+9%) than with G/meanpre (+29%) or with G/peak (+18%). When 6/week treatment time was doubled to 1260 min/week, the gains with G/TAC and G/pre (relative to 3/week with 630 min/week dialysis) were similar (about +94% to 97%), but were lower with G/peak (+55%).

Conclusions. All three equivalent clearances increased on moving from three to six sessions per week, with standard Kt/V having the greatest increase. Standard Kt/V is not at all sensitive to spacing. Alternative clearances based on the TAC or peak concentration have the advantage of taking both spacing and frequency into account.

Keywords: adequacy; daily haemodialysis; haemodialysis; urea kinetic

Introduction

The best way to measure haemodialysis adequacy is a matter of continued interest and debate. The dialysis session Kt/V can be used to compare treatments among patients undergoing the same number of treatments per week, but this approach fails when dialysis needs to be delivered other than three times per week. Also, session Kt/V reflects poorly the removal of solutes other than urea, and high session Kt/V values can be achieved in small patients with very short dialysis treatments.

Various measures have been proposed to quantify weekly haemodialysis dose that would be applicable to different frequencies and durations of dialysis sessions. One equivalent clearance was proposed by Casino and colleagues [1,2]. This measure was analogous to the creatinine clearance measured as U × Qu/P, where U × Qu is the creatinine generation rate [urine creatinine concentration (U) × urine flow rate (Qu)], and P is the plasma creatinine. Because one can derive G, the urea nitrogen generation rate as well as the weekly time-averaged UN concentration (TAC) for any dialysis schedule using modelling, the Casino equivalent clearance that was proposed was calculated as G/TAC. G/TAC, which has units of ml/min, can be translated into a weekly Kt/V by multiplying by 10 080 and dividing by V.

A different idea was proposed by Keshaviah and later refined by Gotch [3–6]. They noted that haemodialysis, automated peritoneal dialysis, and CAPD treatments had similar average predialysis urea concentrations, whereas time-averaged concentrations with APD or haemodialysis were lower than with CAPD. Their approach divided G by the mean predialysis UN rather than by TAC. Again, G/meanpre, in ml/min, can be multiplied by 10 080 and divided by V to get a weekly Kt/V. This resulting ‘standard’ Kt/V is about one-third lower than the corresponding Casino G/TAC clearance, since the mean predialysis UN is usually about one-third higher than TAC. The ‘standard’ Kt/V has the advantage of being similar for clinically determined ‘minimum’ amounts of haemodialysis, APD and CAPD [3–6], and it also takes into account the physiological impact of peak concentration of uraemic toxins.
The ‘standard’ Kt/V has recently gathered some support, and its use has been incorporated into the Clinical Practice Recommendations of the 2006 update to the KDOQI haemodialysis adequacy guidelines [7]. Yet a third measure of clearance might be based on dividing G by the highest UN value seen during the week as opposed to by the average predialysis value.

One issue that has not been critically examined when comparing these various equivalent clearances is how well they would reflect treatment spacing during a given week. Based on clinical common sense, one would expect that three treatments spaced out during the week would be more adequate than three treatments all clustered together. We used a two-pool variable extracellular volume urea kinetic model to compare the effects of treatment spacing on each of these continuous solute clearance measures.

In additional analyses, we compared the ‘gain’ reflected by each of these equivalent clearances by moving from three to six treatments per week (so-called “daily” haemodialysis).

**Materials and methods**

A variable extracellular volume two-pool urea kinetic model was used, as described by Depner [8]. Briefly, urea was modelled as removed from a proximal and a distal compartment, with the clearance between the two, Kc, being a function of post-dialysis urea distribution volume. The volume of the proximal (presumed extracellular) compartment was one-half of the distal (presumed intracellular) compartment. Standard equations were used for dialyser clearance and for the component due to ultrafiltration [8].

It was assumed that post-dialysis urea distribution volume was 35 l, and that the urea nitrogen generation rate (G) was 7 mg/min, and in sensitivity analyses, was also set at 3.5 and 14 mg/min. The intercompartmental clearance, Kc, was set at 560 ml/min. For all treatments, the dialyser diffusive clearance was assumed to be 283 ml/min (blood flow 450 ml/min, dialysate flow 700 ml/min and in vivo dialyser KtA 1064 ml/min, in vitro KtA 776), and this was incremented to reflect additional, convective clearance based on the amount of fluid that needed to be removed. Weekly fluid gain was assumed to be 10 l/week, imbibed at a constant rate during non-dialysis periods. The ultrafiltration rate was set during each treatment to result in a post-dialysis volume of 35 l.

By numerical integration, taking into account volume change due to fluid removal and fluid ingestion, the urea nitrogen concentration of the extracellular and intracellular compartments was computed for each minute throughout the week, and then modelling was continued on for several weeks until the weekly urea nitrogen concentration profile stabilized (usually 3–4 weeks were required for this). At that time, whole-body TAC was computed for the entire week, as well as whole-body predialysis concentrations. This allowed calculation of the various equivalent clearances, which were computed as G/TAC, G/mean predialysis and G/peak, respectively, and then multiplied by 10 080 and divided by 35 000. Although whole body urea nitrogen concentrations were used for these calculations, they differed only minimally from concentrations in the extracellular fluid and therefore plasma water.

**Treatment spacing within a 3/week schedule**

In this first analysis, two 3/week, 210-min treatments were simulated using either a Monday—Tuesday—Wednesday or Monday—Wednesday—Friday schedule. The simulated weekly urea nitrogen profiles are shown in Figures 1 and 2. In these figures, the extracellular fluid concentrations are shown. These were within 1% of the whole body concentrations that were used in the actual computations. Also, all of the concentrations shown in 1 and 2 have been multiplied by 0.93 to better reflect the actual plasma value that would be expected at the various pre- and post-dialysis time points.

**Gain due to more frequent treatments per week, keeping total weekly time constant**

We then simulated the same patient, with a urea nitrogen generation rate of 7 mg/min and a post-dialysis urea distribution volume of 35 l, when given dialysis treatments with the same dialyser clearance using schedules of three or six times per week. In these analyses, the treatments were spaced optimally throughout the week: Monday—Wednesday—Friday for 3/week and Monday through Saturday for 6/week. The weekly dialysis time was held constant at 630 min, and so the session lengths were adjusted to be 210 or 105 min, when treatments were given three or six times per week, respectively.

**Gain due to more frequent treatments per week, keeping session duration constant**

For this analysis, we modelled the same patient (G = 7 mg/min, V = 35 000 ml), given the identical dialysis treatments as above, but each session duration now was kept constant at 210 min, such that the weekly
Table 1. Continuous equivalent clearances with poorly versus well-spaced three dialyses per week

<table>
<thead>
<tr>
<th>Schedule</th>
<th>G/TAC × 10.08/35</th>
<th>G/meanpre × 10.08/35</th>
<th>G/peak × 10.08/35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday—Tuesday—Wednesday (3)</td>
<td>3.18</td>
<td>2.63</td>
<td>1.60</td>
</tr>
<tr>
<td>Monday—Wednesday—Friday (3)</td>
<td>3.83</td>
<td>2.55</td>
<td>2.20</td>
</tr>
<tr>
<td>Percent gain MWF vs. MTuW</td>
<td>+20.2</td>
<td>−3.0</td>
<td>+37.1</td>
</tr>
</tbody>
</table>

MWF = Monday—Wednesday—Friday; MTuW = Monday—Tuesday—Wednesday.

treatment time would increase in direct proportion to the frequency of sessions/week.

Results

Treatment spacing within a 3/week schedule

The TAC was substantially lower during the Monday—Wednesday—Friday treatment schedule compared to the Monday—Tuesday—Wednesday schedule. However, the mean predialysis values during the poorly and well-spaced schedules were quite similar, since the lower predialysis value on Wednesday offset the higher predialysis value on Monday. The peak BUN value, on Monday, was considerably lower with the well-spaced, Monday—Wednesday—Friday schedule, since it was preceded by a much shorter interdialytic interval.

The resulting values for each of the equivalent clearances, G/TAC, G/meanpre and G/peak, always multiplied by 10 080/35 000 to give a weekly Kt/V measure, are shown in Table 1. From the data, it is clear that the percent increase in equivalent clearance, or ‘gain’ associated with the well-spaced versus the poorly spaced schedule, was +20% with G/TAC and +37% with G/peak, but there was no gain at all (∼3%) with G/meanpre (‘standard’ Kt/V).

In a sensitivity analysis, we kept all measures the same, except we set G to be either 3.5 mg/min or 14 mg/min. The results were unchanged.

Gain due to more frequent treatments per week, keeping total weekly time constant

The various equivalent clearances are shown in Table 2. In this case, the percent gain of moving from three to six treatments was lowest with G/TAC (+9.1%), inter-

Table 2. Continuous equivalent clearances with optimally spaced three or six dialyses per week with 630 min/week total treatment time

<table>
<thead>
<tr>
<th>Schedule</th>
<th>G/TAC (ml/min × 10.08/35)</th>
<th>G/meanpre (ml/min × 10.08/35)</th>
<th>G/peak (ml/min × 10.08/35)</th>
<th>Session eKt/V</th>
<th>Session length (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday—Wednesday—Friday (3)</td>
<td>3.83</td>
<td>2.55</td>
<td>2.20</td>
<td>1.44</td>
<td>210</td>
</tr>
<tr>
<td>Monday—Tuesday—Wednesday—Thursday—Friday—Saturday (6)</td>
<td>4.17</td>
<td>3.28</td>
<td>2.59</td>
<td>0.73</td>
<td>105</td>
</tr>
<tr>
<td>Percent gain 6 vs. 3</td>
<td>+9.1</td>
<td>+28.6</td>
<td>+18.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Continuous equivalent clearances with optimally spaced three or six dialyses per week and session length of 210 min

<table>
<thead>
<tr>
<th>Schedule</th>
<th>G/TAC × 10.08/35</th>
<th>G/meanpre × 10.08/35</th>
<th>G/peak × 10.08/35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday—Wednesday—Friday (3)</td>
<td>3.83</td>
<td>2.55</td>
<td>2.20</td>
</tr>
<tr>
<td>Monday—Tuesday—Wednesday—Thursday—Friday—Saturday (6)</td>
<td>7.41</td>
<td>5.07</td>
<td>3.41</td>
</tr>
<tr>
<td>Percent gain 6 vs. 3</td>
<td>+93.6</td>
<td>+99.0</td>
<td>+55.5</td>
</tr>
</tbody>
</table>

mediate with G/peak (+18.0) and greatest for G/meanpre (about +28.6).

Gain due to more frequent treatments per week, keeping session duration constant

In this case, the gain of moving from three to six treatments was similar for G/TAC (+93.6%) and G/meanpre (+99.1%), but was somewhat lower for G/peak (+55.5%) (Table 3).

Discussion

Our results illustrate that the ‘standard’ weekly Kt/V [3–6] exacts no penalty for maldistribution, or lack of spacing, of dialysis treatments during the week. This is because when treatments are clustered together, the low predialysis values of treatments given after very short interdialytic intervals offset the high predialysis values of treatments that follow long interdialytic intervals. So the mean predialysis value changes very little. In contrast, the G/TAC-based equivalent clearance [1,2] does increase when treatments are more optimally spaced out during the week, since TAC urea is then lower. An equivalent clearance based on a G/peak approach showed the greatest sensitivity to optimal spacing, since even a single longer interdialytic interval greatly increases the peak urea nitrogen value.

All of these analyses were done assuming the same urea generation rate, 7 mg/min, and G was constant throughout the week. This means that the weekly total solute removal with all of the sessions modelled was the same, 7 × 10 080 = 70 560 mg/week. Total solute removal per se is not a good way to compare different dialysis schedules, since at steady state, weekly solute removal simply reflects the generation rate of that solute. What more intensive dialysis regimens do accomplish is to lower the time averaged as
Effect of treatment spacing and frequency on three measures of equivalent clearance, including standard Kt/V well as peak concentrations of solutes such as urea, and this is what is believed to be key to mitigating the abnormalities seen in the uraemic condition.

The argument about whether peak or time-averaged uraemic toxin concentration is of greater importance, as first advanced by Keshaviah [1], remains largely unresolved. The seeming equivalence between minimum weekly ‘standard’ haemodialysis Kt/V and minimum weekly peritoneal Kt/V [3–6] does not necessarily support a peak toxin concentration hypothesis, as the clinically determined minimally adequate weekly Kt/V value for peritoneal dialysis may be due to other factors. For example, weekly doses of peritoneal dialysis >2.0/week might ordinarily give better outcomes, except for the fact that with peritoneal dialysis an increase in dose must almost always be bought at the expense of subjecting the patient to a larger glucose load or to higher intraperitoneal fluid volumes, and the last two, particularly glucose load, may adversely impact outcomes, counterbalancing any benefit of increased solute clearance.

One argument in favour of judging adequacy using ‘standard’ Kt/V instead of G/TAC might be the larger ‘gain’ seen when moving from 3 to 6/week dialysis when total weekly time is kept constant (+28.6% with ‘standard Kt/V versus +9.1% with G/TAC). The gain in G/TAC on moving from three to six treatments was related to equilibrated Kt/V (eKt/V), and was even smaller at lower levels of eKt/V (data not shown). The gain with G/peak (+18%) was intermediate between the other two measures.

In conclusion, although the ‘standard’ Kt/V measure does historically come up with similar values for minimally adequate haemodialysis and peritoneal dialysis, the inability of ‘standard’ Kt/V to reflect treatment dispersion throughout the week should be kept in mind. Use of an equivalent clearance based on G/peak or some different method might be alternative approaches worth exploring. Finally, dialysis frequency may well be of key importance in removal of uraemic toxins such as phosphate as well as non-urea-based toxins [9], and the ‘gain’ in adequacy associated with increasing frequency from three to six treatments per week may well exceed that suggested by any one of these urea-based equivalent clearances.

Conflict of interest statement. None declared.

References


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