Effect of treatment frequency on haemodialysis dose: comparison of EKR and stdKt/V

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Abstract

Background. Haemodialysis outcome cannot be improved by increasing the dialysis session dose above the current standard in conventional schedules. Promising results have been reported from daily dialysis, but the optimal dose has not been established.

Methods. Weekly eKt/V, equivalent renal clearance (EKR) and stdKt/V were compared retrospectively in 588 complete urea kinetic modelling sessions of 35 haemodialysis patients. Equivalent values of EKR and stdKt/V corresponding to the standard and high doses of the HEMO study were defined by computer simulation. The effect of frequency on the dose measures was demonstrated by simulating different schedules.

Results. EKR and stdKt/V take into consideration both frequency and RRF, but appreciate them differently. The values of EKRc (EKR in millilitres per minute, normalized to distribution volume 40 l), stdEKR (EKR in litres per week divided by urea distribution volume in litres) and stdKt/V corresponding to eKt/V 1.20—close to the standard dose in the HEMO study were 13.2 ml/min/40 l, 3.34/wk and 2.23/wk, respectively. stdKt/V appreciates frequency more than EKR. A spreadsheet was created to compute the dialysis session time to achieve the EKR or stdKt/V target when the basic urea kinetic variables are known.

Conclusions. Haemodialysis efficiency can be increased by increasing frequency. EKR and stdKt/V are more appropriate than weekly eKt/V as measures of dialysis dose in different schedules. With increasing frequency, stdKt/V as the dosing target results in shorter treatment times and higher concentrations than EKR.

Keywords: computer simulation; dialysis dosing; EKR; eKt/V; stdKt/V

Introduction

According to the HEMO study [1], the outcome of haemodialysis (HD) cannot be improved by increasing the session dose (Kt/V) above the current standard of a three times per week schedule.
Chen et al. [7] observed that weekly Kt/V values of CAPD patients and weekly URRs of HD patients were similar to each other. Cheng et al. [10] reported higher weekly URR values for CAPD than for HD patients despite markedly higher wKt/V in HD. Maduell et al. [5] and Williams et al. [6] observed higher weekly URR in short daily than in conventional treatment with the same weekly treatment time and wKt/V or weKt/V.

The optimal dose measure for schedules other than three times weekly has not been established [15]. The European guidelines [16] recommend stdKt/V, EKR and SRI. Unfortunately, SRI has conflicting definitions.

The objective of the current retrospective observational analysis is

1. to determine the EKR and stdKt/V values corresponding to the standard and high doses of the HEMO study and
2. to compare EKR and stdKt/V as measures of dialysis dose in symmetric schedules with different frequencies.

Subjects and methods

Detailed description of the abbreviations, symbols, definitions and equations is presented in the Appendix.

Data have been gathered by a dialysis information system in the routine care of HD patients. No randomization, control group or study protocol has been used.

Urea kinetic modelling with three blood samples and interdialysis urine collection was done once per month (modelling session). Postdialysis blood samples were taken at the termination of the session with a modified KDOQI slow-blood-flow technique [17]. Postdialysis urea concentrations were converted to equilibrated ones by the Tattersall method [18]. Then all calculations were done using the classic single-pool variable-volume urea kinetic model (spvvUKM) [19,20] with the equilibrated postdialysis values. The urea generation rate (G) and distribution volume (V) are required in computing the protein equivalent of total nitrogen appearance (nPNA), EKR and stdKt/V.

Dialysis sessions

The analysis is based on 588 data sets collected between 1 January 2004 and 31 December 2006 from 35 prevalent HD patients having at least one complete urea kinetic modelling session after the first 4 weeks of dialysis. All patients were white Europeans. The modelling sessions are described in Table 1.

Residual renal function (RRF)

RRF is expressed as renal urea clearance Kr (ml/min) and renal fractional urea clearance rFC (/wk). The entire interdialysis urine was collected. The calculation of Kr is described in the Appendix. If Kr was below 1 ml/min in three consecutive measurements, Kr and diuresis were stated as zero and urine was not collected in subsequent modelling sessions.

Dialysis dose

All variables, including G, Vt, Kr, rFC, nPNA, EKR and std/V, are based on equilibrated postdialysis concentrations although explicitly noted only on eKt/V.

Dialysis dosing is expressed in four ways:

1. EKRc: EKR normalized to distribution volume of 40 l, expressed in ml/min units (Casino and Lopez)
2. stdEKR: EKR divided by distribution volume, expressed in /wk units to facilitate comparison to stdKt/V
3. stdKt/V (Gotch) in /wk units

4. weekly eKt/V: the sum of the eKt/Vs of 1-week treatment sessions, in /wk units.

Time-averaged concentration (TAC) and average predialysis concentration (PAC), needed in calculating EKR and stdKt/V, cannot be derived from a single modelling session. Treatment parameters were averaged over 4 weeks preceding and including the modelling session. The actual dialysate urea clearance (Kd) of each treatment was calculated from actual blood and dialysate flow (Qb, Qd) and the mass transfer area coefficient (KoA) of the dialyser [21]. KoA is based on several blood side blood water clearance measurements of each dialyser model. Dialysers were used only once.

Treatments were equalized by iterating the spvvUKM concentration equation [19] sequentially over average treatment time and average interval time until plateauing of the predialysis concentration (see the Appendix). This procedure modifies an asymmetric schedule to an evenly distributed one, but has no influence on the patient-specific values.

Simulations

The effect of treatment frequency on the measures of dialysis dose was studied by computer simulations. They are based on the classic spvvUKM with the patient-dependent values G, Vt and Kr from the modelling session and varying treatment values, keeping weekly ultrafiltration unchanged and assuming that dialysis has no effect on urea generation and renal function.

Statistical methods

Microsoft Excel 2002 software was used in calculating minimum and maximum values and standard deviations and in creating the graphs.

Results

Equivalent doses

Equivalent values corresponding to the standard and high dialysis doses of the HEMO study were determined by simulating a conventional dialysis with a symmetric 3 × 4 h/wk schedule and eKt/V 1.20 and 1.60 in the study material (Table 2), respectively. Dialysis intensity was adjusted by dialyser clearance. Numbers in the table are averages of the 588 sessions. The most important parameters are in bold.

The simulated values of EKRc, stdEKR and stdKt/V corresponding to eKt/V 1.20—close to the standard dose in the HEMO study (1.16)—are 13.2 ml/min/40 l, 3.34/wk and

<table>
<thead>
<tr>
<th>Table 1. Modelling sessions</th>
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<tbody>
<tr>
<td>Data</td>
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<td>Renal urea clearance</td>
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<td>Renal fractional urea</td>
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Effect of treatment frequency on haemodialysis dose

Table 2. Average equivalent measures of HEMO standard and high doses

<table>
<thead>
<tr>
<th>Data</th>
<th>Unit</th>
<th>Actual equalized</th>
<th>HEMO standard 3 × 4 h</th>
<th>HEMO high 3 × 5 h</th>
<th>HEMO high 6 × 2.5 h</th>
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2.23/wk, respectively. Weekly eKt/V and stdEKR are remarkably higher than stdKt/V, far above the range achieved in CAPD. The values of EKRc, stdEKR and stdKt/V corresponding to eKt/V 1.60—close to the high dose in the HEMO study (1.53)—are 16.4 ml/min/40 l, 4.14/wk and 2.54/wk, respectively.

It may be difficult to achieve eKt/V 1.60 in 4 h. The last two columns of Table 2 represent the HEMO high dose equivalent values in symmetric 3 × 5 h/wk and 6 × 2.5 h/wk schedules, respectively. Uraemic toxicity is probably related to concentrations. Predialysis and TACs are lower with higher frequency, although generation and elimination rates, treatment time and dialysis fluid consumption are equal. This may be interpreted as better efficiency and is reflected in higher EKR and stdKt/V, but not in weKt/V.

Effect of frequency

The simulations are based on weekly eKt/V, stdEKR and stdKt/V as measures of dialysis dose.

Figure 1 describes the effect of frequency on different measures of dialysis dose in a patient with average characteristics of the study material (Table 1). Frequency affects stdKt/V more than stdEKR. Weekly eKt/V is not dependent on frequency.

Figures 2–4 represent the patient dialysed with the standard-equivalent doses defined in Table 2.

Figure 2 describes the effect of frequency on the weekly treatment time required to achieve the standard-equivalent doses with constant Kd. Much more time is needed to achieve the stdKt/V target in a two times per week schedule than in three times per week. The effect of frequency is less steep with stdEKR as the target dose measure.

With higher frequency, using stdKt/V as the target results in higher concentrations (C0 and TAC) than stdEKR (Figures 3 and 4).

The curves in Figures 1–4 are based on a simulated patient with G = 218 μmol/min, V = 40.0 l, Kr = 0.65 ml/min (Table 1) and UF = 8.5 l/wk (Table 2). With the spreadsheet DoseOpt.xls in http://www.verkkomunua

Discussion

The current analysis is based on the UKM. One of the parameters in this model is renal urea clearance, which is lower than the glomerular filtration rate.

HD urea kinetics can be described rather accurately by a two-pool model that requires several blood samples or a dialysate urea monitor. Using single-pool UKM with dialyser clearance and equilibrated postdialysis concentration as input parameters is a practical shortcut, although incorrect in theory. It involves mixing of single- and double-pool models and overestimates Vt to compensate the difference between dialyser clearance and whole body patient clearance to give a ‘correct’ eKt/V. This concept was used as the
reference in a HEMO pilot study in choosing the method to measure the delivered dialysis dose [22]. Inaccuracy of the single-pool model affects the equalization procedure and simulations in the current study.

The current material differs in several aspects (age, weight, race, sex distribution, anthropometric total body water, maximum rFC) from the HEMO study. In a different population, the values of EKR and stdKt/V corresponding to eKt/V 1.2 and 1.6 may be different.

Weekly measures of dialysis dose are required in comparing different schedules, but as seen from Table 2 and the figures and argued in the literature [13,14], weekly eKt/V underestimates the therapeutic significance of frequency.

In CAPD, stdKt/V and stdEKR are equal to the fractional clearance ("weekly Kt/V"). In standard HEMO-equivalent dialysis (Table 2), the average stdKt/V (2.23 /wk) is comparable to the stdKt/V of CAPD patients. Possibly the greater unphysiology (fluctuation of volume and concentrations, compartment disequilibrium) and different sieving profiles of the membrane have to be compensated by a slightly greater dose in HD to achieve equal outcome.

According to the European guidelines [16], in anuric patients, treated by three times per week dialysis, the prescribed target eKt/V should be at least 1.2, and for patients with renal function or those with dialysis schedules other than three times per week, weekly dialysis dose should be at least equivalent to an SRI of 2. In a symmetric schedule, SRI—as defined in the guidelines—is equal to stdKt/V. In the current material, the SRI or stdKt/V value corresponding to a delivered eKt/V of 1.2 is considerably higher. The difference corresponds to 42 min of session time (198 versus 240 min) in a symmetric three times per week schedule with a Kd of 200 ml/min. SRI 2.00/wk corresponds to eKt/V 0.99. With significant RRF, a lower value of SRI or stdKt/V may be acceptable, because it, based on the UKM, underestimates renal function.

Future investigation is needed to elucidate whether increasing the dialysis dose above the equivalents of the HEMO standard dose by increasing the frequency is of any prognostic benefit and whether increased dose or decreased unphysiology [23] is more important in frequent dialysis.

stdKt/V appreciates frequency more than EKR. If diminished unphysiology is the most essential advantage of frequent dialysis, then dosing is best guided by stdKt/V resulting in shorter weekly treatment time with increasing frequency, but if dose is important, then EKR is more suitable resulting in lower concentrations.

Conflict of interest statement. None declared.
Appendix

Abbreviations and symbols
UKM = urea kinetic model
spvvUKM = single-pool variable volume UKM
RRF = residual renal function
HD = haemodialysis
CAPD = continuous ambulatory peritoneal dialysis
Qb = blood flow
Qd = dialysate flow
t = observation period duration
td = dialysis session duration
ti = dialysis interval duration
fr = dialysis session frequency
G = generation rate
E = removal rate
K = clearance
Kd = diffusive blood water dialyser clearance
KoA = mass transfer area coefficient of the dialyser
Kr = renal clearance
rFC = renal fractional clearance
C = concentration
C1 = concentration at the beginning of the observation period
C2 = concentration at the end of the observation period
C0 = concentration at the beginning of a dialysis session
Ct = equilibrated postdialysis concentration
C02 = concentration at the beginning of the next dialysis session
TAC = time-averaged concentration, computed using equilibrated postdialysis concentration
PAC = average predialysis concentration, average C0
Cu = urine concentration
V = distribution volume
V1 = distribution volume at the beginning of the observation period
V0 = distribution volume at the beginning of a dialysis session
Vt = distribution volume at the end of a dialysis session
Vo2 = distribution volume at the beginning of the next dialysis session
Va = average distribution volume
Vu = interdialysis urine volume
VG = fluid accumulation during the observation period
VGD = fluid accumulation during a dialysis session, usually negative
VGi = fluid accumulation between dialysis sessions
WGi = weight gain between dialysis sessions
UF = ultrafiltration volume (positive, if fluid is removed)
URR = urea reduction ratio
SRI = solute removal index
FSR = fractional solute removal
tFSRR = average total fractional solute removal rate (renal + dialysis)
wFSR = weekly total fractional solute removal (renal + dialysis)
RUR = renal urea removal, amount of urea in interdialysis urine
DUR = amount of urea removed in a dialysis session
Kt/V = dialysis session dose, single pool

\begin{align*}
eKt/V & = \text{equilibrated dialysis session dose} \\
wKt/V & = \text{weekly } Kt/V \\
weKt/V & = \text{weekly } eKt/V \\
EKR & = \text{equivalent renal urea clearance, a measure of dialysis dosing defined by Casino and Lopez} \ [12] \\
EKRc & = \text{EKR normalized to a urea distribution volume of } 401 \\
\text{stdKt/V} & = \text{a measure of dialysis dosing defined by Gotch} \ [13] \\
\text{stdEKR} & = \text{EKR divided by } V; \text{ comparable to stdKt/V} \\
NBW & = \text{normal body weight} \\
PNA & = \text{protein equivalent of total nitrogen appearance} \\
nPNA & = \text{normalized PNA}
\end{align*}

Definitions and calculations

\begin{align*}
VGi & = WGi \quad \text{(in conjunction with the actual modelling session)} \quad (A.1) \\
VGi & = UF \quad \text{(in the equalized schedule)} \quad (A.2) \\
VGd & = -UF \\
V0 & = Vt + UF \\
V02 & = Vt + VGi \\
Vt & = (V0 + Vt)/2 \\
RUR & = Vu^rCu \\
DUR & = V0^rC0 - Vt^rCt + td^rG \\
G & = (V0^rC0_2 - Vt^rCt + RUR)/ti \\
rFC & = Kr/Vt \\
Kt/V & = Kd^rtd/Vt \\
wKt/V & = fr^rKt/V \\
weKt/V & = fr^rEkt/V \\
nKt/V & = 0.92^rfr^r(1 - \exp(-1.1^rKt/V)) \\
NBW & = Vt/0.58 \quad \text{(assuming 1 litre weighs 1 kg)} \quad (A.15) \\
nPNA & = PNA/NBW. \quad (A.16)
\end{align*}

The Sargent modification \ [24] of the original Borah equation \ [25] was used in calculating PNA.

EKR (equivalent renal urea clearance) and stdKt/V are based on the definition of clearance:

\begin{align*}
K & = E/C. \quad (A.17) \\
\text{In steady state } E & = G, \quad \text{so} \\
K & = G/C. \quad (A.18)
\end{align*}

In EKR, the term C of equation \ (A.18) is the time-averaged concentration \ (TAC), in stdKt/V, the average predialysis concentration \ (PAC). According to the definition, stdKt/V
is normalized by dividing the value of equation (A.18) by the distribution volume \( V \). Dividing \( EKR \) by \( V \) yields a variable called here as stdEKR (eqKt/V in [26]):

\[
\text{stdEKR} = \frac{G}{TAC/Va} \quad (A.19)
\]

\[
\text{stdKt/V} = \frac{G}{PAC/V0}. \quad (A.20)
\]

The unit of stdEKR and stdKt/V is \( /wk \). To ensure conformity with wtFSR, predialysis volume \( V0 \) is used in stdKt/V, average volume \( (Va) \) in stdEKR.

EKRe is stdKt/V multiplied by a ‘normal’ distribution volume 40 l and divided by the number of minutes in a week (10 080) [12]:

\[
\text{EKRe} = 3.97^{\ast}\text{stdEKR}. \quad (A.21)
\]

The unit of EKRe is \( \text{ml/min}/40\text{l} \).

Weekly total fractional solute removal (wtFSR) is the amount of urea removed by dialysis and the kidneys during 1 week divided by the average predialysis amount of urea in the body. More generally

\[
fK(Ct, C02, Vt, ‘\text{computation of clearance by binary search}') = \text{Kr}. \quad (A.23)
\]

Repeat
\[
K = (K1 + K2)/2
\]
\[
Cc = fCt(C1, V1, VG, t, K, G)
\]
If \( Cc > C2 \) Then
\[
K1 = K
\]
Else
\[
K2 = K
\]
End If
Until \( \text{Abs}(Cc - C2)/C2 < 0.00001 \)
\[
fK = K.
\]

**Equalizing the schedule to a symmetric one**

In column ‘Actual equalized’ of Table 2, dialysis frequency, dialysis time, weekly dialysis time, dialyser clearance, ultrafiltration volume, equilibrated Kt/V and weekly equilibrated Kt/V are averages of the 4-week averages associated with each modelling session.

Treatments are equalized by iterating the classic spvvUKM concentration equation sequentially over the average treatment time and average interval time until plateauing of \( C0 \), using \( Kr, Vt \) and the modelling session and average \( Kd \) and average UF:

\[
C0 = \text{ASV} \quad ‘\text{arbitrary starting value}'.$
\]

Repeat
\[
Cp = \text{C0} \quad ‘\text{previous C0}'.$
\]
\[
Ct = fCt(C0, Vt+AvgUF, \quad ‘\text{spvvUKM concentration equation, dialysis}'.$
\]
\[
\text{AvgKd, Kr, G})
\]
\[
C0 = fCt(C1, Vt, AvgUF, \quad ‘\text{spvvUKM concentration equation, interval}'.$
\]
\[
\text{Avgti, 0, Kr, G})
\]
Until \( \text{Abs}(C0 - Cp)/C0 < 0.00001 \)

The equalization procedure modifies \( C0 \) and \( Ct \) and facilitates calculations of TAC, PAC, EKR, stdKt/V and wtFSR. PAC is \( C0 \) computed by equalizing. TAC is the cycle area_under_the_time/concentration_curve divided by the cycle duration, calculated from the equalized values according to Casino and Lopez [12]. RUR is calculated by multiplying the equalized interdialysis area_under_the_time/concentration_curve (used in TAC calculation) by \( Kr \). In a symmetric schedule,

\[
\text{wtFSR} = f^\ast(RUR + DUR)/(C0^\ast V0). \quad (A.23)
\]

The FSR concept enables assessment of the renal and dialysis components of urea elimination separately without dialysate collection.

**References**


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**The impact of dialysis modality on skin hyperpigmentation in haemodialysis patients**

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Both the authors contributed equally to this work.

**Abstract**

**Background.** Skin hyperpigmentation in end-stage renal disease (ESRD) patients has been attributed to the accumulation of middle-molecular-weight (MMW) substances. Although an MMW mechanism suggests that hyperpigmentation may be improved by high-flux haemodialysis (HF-HD) and haemodiafiltration (HDF), this possibility has not been explored. In the present study, we investigated the impact of different dialysis modalities on skin colour in HD patients.

**Methods.** Eighty-two ESRD patients on HD were divided into low-flux HD (LF-HD), HF-HD and HDF groups. The melanin index (MI) and erythema index (EI) of the abdomen and the flexor side of the forearm (non-sun-exposed areas) and the forehead (sun-exposed area) were determined by using a narrow-band reflectance spectrophotometer at baseline and after 12 months.

**Results.** Even though absolute values of baseline and follow-up MI and EI of the three sites were comparable among the three groups, forehead MI and EI were significantly decreased after 12 months in the HDF group ($P < 0.05$). In addition, the change in forehead MI was significantly greater in the HDF than in the LF-HD group (-1.0 ± 2.4% versus 0.3 ± 1.6%, $P < 0.05$). Moreover, $\beta_2$-microglobulin reduction rates were negatively correlated with both changes in forehead MI ($P < 0.01$) and EI ($P < 0.05$).

**Conclusions.** Skin colour of sun-exposed areas was significantly decreased in ESRD patients receiving HDF therapy, suggesting that enhanced removal of MMW substances by convection may prevent or reduce hyperpigmentation in HD patients.

**Keywords:** $\beta_2$-microglobulin; haemodiafiltration; hyperpigmentation; low-flux haemodialysis; spectrophotometer