Optimization of haemodialysis frequency and duration. A computer simulation study

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Introduction

Haemodialysis (HD) is a specific treatment for uraemia, consisting of multiple doses administered rhythmically at time intervals not all equally spaced. It can be used for only 5–9% of the lifetime of the uraemic patients and, therefore, it must be properly planned to ensure acceptable relief of the uraemic syndrome. However, the design of a good HD schedule is empirical, since the concepts of HD dose and adequacy are not completely agreed upon.

The importance of the urea kinetic modelling approach in evaluation of HD was the main conclusion of the National Cooperative Dialysis Study (NCDS) [1], as perhaps should have been expected, considering the fluctuating profiles of urea in the blood of uraemic patients. The NCDS conclusions emphasized the importance of the time-averaged plasma urea concentration (TAC) as a predictor of a good outcome. TAC urea includes removal of urea from the body and its production, and thus may be considered a measure of the urea balance, provided that body volumes are not grossly changed. In the following mechanistic analysis of the NCDS data [2], Kd*t/V was proposed as a quantitative estimation of HD dose, in which Kd is the urea clearance of the haemodialyser, t is the time duration of HD, and V is the volume distribution of the urea. Kd*t/V is a dimensionless number which arises from analytical solution of ordinary differential equations of the single-pool urea model and has clinical meaning on its own. Neither TAC urea nor Kd*t/V enable us to separate production of urea (represented by the protein catabolic rate in patients on nitrogen balance) from its removal.

The characteristics of the HD procedure can be dealt with by the technique of simulation modelling, which, with the advent of the computers, is an invaluable tool in many fields of science and research. However, there are a few features specific for HD which cause some difficulties to the modeller: the intervals between treatments are not equally spaced; the operative parameters can change during the procedure; too few assumptions, sometimes difficult to be met in practice, are required for the system to be fully managed; and good system identification is far from being attained.

The aims of the present study were to forecast the urea concentration profile and TAC urea over time by computer simulation in a single-compartment variable volume (SPVV) model. The effects on TAC urea and Kd*t/V of two HD schedules, the traditional alternate day HD and daily HD, each with three different HD durations, were compared at the steady state condition. The importance of achieving the steady state for adequate comparisons is emphasized.

Subjects and methods

The patient–haemodialysis system was described as a one-compartment variable volume (Vt) system, in which a diffusive first-order process takes place intermittently for a fixed time interval (td) and at a fixed frequency. The assumptions of instantaneous and complete mixing inside the compartment are assured by definition. The equations of the model are shown in the Appendix. The analytical solutions of the model equations are detailed in [3]. The initial compartment volume (V0) was set at 38 l. During two consecutive HD, the Vt increased at a constant rate so that the same V0 was reached at the end of the interval (td). The initial plasma urea concentration (C0) was 180 mg/dl. A urea generation rate (Gu) of 8.0 mg/min was assumed to follow zero-order kinetics. The HD filter was modelled as a subsystem with concentrated parameters, characterized by a clearance (Kd) of 160 ml/min and an ultrafiltration rate (UFR) of 10 ml/min during HD. Two HD regimens were planned, as follows: one daily regimen with td of 90, 120 and 150 min, and a traditional alternate day regimen with td of 180, 240 and 300 min. The fixed HD were assumed to be equally spaced.

TAC urea was calculated for the interval td + td by dividing the definite integral of the C function curve, equivalent to the area under the curve, by the time elapsed. Kd*t/V was calculated as the logarithm of the ratio between initial C0 and end-dialysis Cc. Each simulation was run in cycles of 48 h. The patient–haemodialysis system was considered to be in a steady state condition when C0 was constant in successive runs. All simulations were performed with Mathcad 5.0 by MathSoft, Inc., Cambridge (Ma), USA, running on PC-Windows.
Results

When the model was run with the chosen parameters, the typical plasma urea profile, with a sudden reduction of the plasma urea concentration in the HD period and an increase at constant rate between HD sessions, was obtained. The rate of weight gain between HD sessions was adjusted so that $V_t$ was the same at the beginning of the next HD.

First simulation setting

Initially, simulations lasting only 48 h were performed, using the two HD regimens with the same $G_u$ of 8.0 mg/min. The results of this simulation are summarized in Table 1, in which the TAC urea, $K_t/V$ and the initial $C_i$ at the next HD are shown. All the TAC urea were lower, and all the $C_i$ higher at 48 h on the alternate day regimen than on the daily regimen. In both regimens, TAC urea decreased with increasing $t_d$; on the alternate day regimen, it ranged from 157 to 128 mg/dl, and on the daily regimen from 164 to 132 mg/ml. In the same way, $C_i$ decreased with increasing $t_d$, being 195, 171 and 151 mg/dl on daily HD, and 219, 202 and 188 mg/dl on the alternate day HD. Calculated $K_t/V$ values increased as $t_d$ increased, being 0.690, 0.908 and 1.119 on the alternate day regimen, and 0.350, 0.465 and 0.578 on the daily regimen.

Second simulation setting

As forecast, after 48 h, the $C_i$ was different from the starting value of 180 mg/dl (Table 1) and the steady state condition was not achieved with the first simulation setting. Therefore, a new experimental parameter set was applied: $K_d$ and $V_o$ were left unchanged and $G_u$ was lowered progressively, starting from 8.0 mg/min, to reach the steady state of urea balance at 48 h on the alternate day HD regimen. Continuing by trial and error, with $t_d$ of 180, 240 and 300 min, the $C_o$ at 48 h became 180 mg/dl at $G_u$ of 5.7, 6.7 and 7.5 mg/min, the corresponding TAC ureas were 137, 129 and 124 mg/dl, and the corresponding $K_d*t/V$ were 0.708, 0.923 and 1.127 (Table 2).

These new $G_u$ values were then fed into the corresponding daily HD regimens and a new series of simulations was run to obtain $C_o$, $K_d*t/V$ and TAC urea at the steady state. The $t_d$ of the daily HD regimen was halved. The results at the targeted steady state are shown in Table 2: at $t_d$ 90, 120 and 140 min, the $C_o$ was 148, 140, and 132 mg/dl; the TAC urea was 129, 118 and 109 mg/dl; and the $K_t/V$ was 0.354, 0.462 and 0.564.

The steady state was reached at progressively increasing $t_d$ rates ranging from 90 to 150 min, resulting in six cycles in the $t_d$ of 90 min, five cycles in the $t_d$ of 120 min and four cycles in the $t_d$ of 150 min. Figure 1 shows all the intermediate steps of the simulated urea profiles on 300 min alternate day HD and 150 min daily HD.

Third simulation setting

The last series of simulations was run on the daily HD regimen, with the aim of achieving the steady state condition at the same TAC urea as with the corresponding alternate day HD regimen, as shown in Table 2. The same starting $C_o$ of 180 mg/dl was chosen, $G_u$ were

### Table 1. Results of the first simulation setting

<table>
<thead>
<tr>
<th>Alternate day haemodialysis</th>
<th>Daily haemodialysis</th>
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</thead>
<tbody>
<tr>
<td>HD duration (min)</td>
<td>TAC (mg/dl)</td>
</tr>
<tr>
<td>180</td>
<td>157</td>
</tr>
<tr>
<td>240</td>
<td>140</td>
</tr>
<tr>
<td>300</td>
<td>128</td>
</tr>
</tbody>
</table>

Simulation duration was 48 h and $G_u$ 8.0 mg/min. $K_d*t/V$ was calculated for a single HD.

### Table 2. Results of the second simulation setting

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</tr>
</tbody>
</table>

Simulation duration was 48 h $K_d*t/V$ was calculated for a single HD. $G_u$ was 5.7 mg/min for 90 and 180 min HD, 6.7 mg/min for 120 and 240 min HD, and 7.5 mg/min for 150 and 300 min HD.
A computer simulation study on optimization of haemodialysis

urea and \( C_0 \) were lower on the daily regimen (Table 2). If, on the other hand, the same TAC urea of the alternate day regimen was targeted on the daily regimen, the durations of HD would have been reduced from 90 to 85, from 120 to 108, and from 150 to 130 min. The longer the HD, the more time was saved.

The algorithm used for optimizing the HD time is represented in Figure 3. It finds the \( t_d \) of the daily HD which provides the same TAC urea as the corresponding alternate day regimen through repeated iterations until the steady state is reached. The TAC urea is then evaluated and, if it is different from the targeted value, a new \( t_d \) is chosen and a new cycle is started.

A typical feature of the daily regimen is the more flattened urea plasma profiles, with smaller peaks and troughs. Whether or not this urea pattern has more beneficial effects on the uraemia, independently of the lower TAC urea and the same HD duration per week, TAC urea, remains to be ascertained [4].

The Kd*\( t/V \) was calculated at the steady state for a fixed as previously shown in Table 2, and \( t_d \) was left as the only variable. The output of the simulation produced the targeted TAC ureas at \( t_d \) of 85, 108 and 130 min with steady state \( C_0 \)s of 156, 152 and 147 mg/dl and K*\( t/V \)s of 0.335, 0.419 and 496. Figure 2 shows the simulation course for achieving the same TAC urea of 123 mg/dl at the optimal \( t_d \) of 130 min.

**Discussion**

HD simulation enables nephrologists to manipulate parameters and variables of the treatment and investigate results almost immediately. This is useful, especially when the conditions are difficult or even dangerous to carry out in usual medical settings. Moreover, the parameters and variables are under the control of the modeller, so the results can be causally related to specific sources. Sensitivity of the parameters can also be tested. However, modelling HD regimens is more complex than modelling isolated HD, and adequate methods must be used.

In the first simulation experiment, lasting 48 h, higher TAC urea values were obtained on all three daily regimens (Table 1). When simulation was run repeatedly until the steady state was reached, the TAC urea and \( C_0 \) were lower on the daily regimen (Table 2).

**Algorithm of Simulation**

```
Fix Parameters G1, V, t1, TAC1

G2 = G1

t2 = 1/2 t1

Run Simulation

C0 = C0 (t1)

If TAC2 = TAC1

Yes

DECREASE t2

OUTPUT T2, TAC2, C0

No
```

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1. Plasma urea profile in the 300 min alternate day (top line) and 150 min daily HD (bottom line) regimens. The HD duration was the variable \( G_u \) 7.5 mg/min. The dotted lines indicate the steady state \( C_0 \). The same TAC urea was reached after reducing HD time from 150 to 130 min in the fifth cycle.

2. Plasma urea profile in the 300 min alternate day (top line) and daily HD (bottom line) regimens. The HD duration was the variable \( G_u \) 7.5 mg/min. The dotted lines indicate the steady state \( C_0 \). The same TAC urea was reached after reducing HD time from 150 to 130 min in the fifth cycle.
In conclusion, we think that simulation modelling in HD can be useful for ‘scenario’ or ‘what if’ analysis, especially for complex situations. The results of the simulations must be viewed as educated guesses to be validated with planned investigations. Therefore, care must be taken when extrapolating simulation results into the clinical setting.

Appendix

Equations of the SPV model

**HD period:**

\[
\frac{d(V_t \cdot C_t)}{dt} = G - Kd \cdot C_t
\]

**ID period:**

\[
\frac{dN_t}{dt} = -UFR
\]

### References


