A Mathematical Single-Pool Model for Short Time Haemodialysis

T-E WIDERØE, L GRIMSRUD, K J BERG, A GODAL, R JENSEN, S JØRSTAD

Regional Hospital in Trondheim, and Institute of Thermodynamics, University of Trondheim, Norway

Summary

The objective was to reduce treatment time while the average concentration of all molecular sizes was maintained equal to that in a standard treatment. A nomogram based on the one-pool patient-dialyser system has been devised. The patient variables are presented in dimensionless forms, thus making one diagram suffice for all patients and all molecular sizes.

Seven patients were first observed during a standard programme and later during an individually calculated short-time programme. The clinical parameters indicated equal treatment. The method was practical enough for clinical use.

Introduction

The success of chronic haemodialysis in maintaining life is really astonishing since we do not know which components of blood to take out and which to retain. To further complicate matters, we do not even have an objective indicator as to what constitutes adequate treatment.

After the introduction of analogue simulation of the patient-artificial kidney system (Bell et al, 1965) and later the introduction of a theory on how to remove molecules within a preselected molecular weight range (Babb et al, 1971), several analytical models for quantification of dialysis treatment have been suggested (Babb et al, 1972; Edson et al, 1972; Kjellstrand et al, 1972; Sargent et al, 1973). Several investigators have used these models as guidelines (Ginn et al, 1971; Christopher et al, 1971; Cambi et al, 1972; Millora et al, 1972; Kjellstrand et al, 1973). The results of different treatment schedules concerning the influence of large, middle and small molecules on the well being of the patient are in many cases conflicting and controversial.

These conflicting reports are not surprising. Not only have the experimenters not controlled and compensated for the more obvious variables like patient
One-pool patient-dialyser model

Blood concentration variations during and between treatments

Weekly blood concentration variation

\[ C_i = 150 \text{ mg}\% \quad T = 48 \text{ h} \quad t = 4 \text{ h} \]
\[ M = 70 \text{ kg} \quad G = 1.8 \text{ mg%/h} \quad K = 145 \text{ ml/min} \]

Figure 1. Single-pool patient-dialyser model (a) and blood concentration variation with time, (b) and (c).
weight, toxin production rates and dietary intake, we also do not know what most of the variables are.

Couple these factors with individual patient tolerance, and the chance of determining the nature of the offending molecules by varying the treatment schedules becomes rather remote.

Appreciating these facts but at the same time recognizing the importance of a shortened treatment time, it has been the objective of this work to show how treatment time can be reduced while the quality of the treatment is maintained equal to that of a standard treatment. Quality here means maintaining the average concentration levels of all molecular sizes essentially unaltered. To be of any use the method has to be accurate and practical enough for clinical routine.

METHODS OF CALCULATION

We have devised a nomogram based on the familiar one-pool patient-dialyser system (Figure 1a). The patient variables are presented in dimensionless form, thus making one diagram suffice for all patients (Figure 2).

![Nomogram giving relationship between parameters in single-pool patient-dialyser model.](image)

Figure 2 can be used in the following manner: Patient data must be known, i.e. weight and accumulation rate of urea. The last can be found by taking the difference between the patients post-dialysis and pre-dialysis values and dividing this result by the number of hours between the two samples. This compensates
for residual kidney function, and eliminates the need for two sets of equations, with and without residual kidney function. $G$ is therefore called accumulation rate instead of the customary production rate. On the basis of experience or data from earlier long-time dialysis, a maximum permissible concentration, $C_i$, is chosen. The desired schedule is then selected, for example $T = 48$ hr and $t = 4$ hr. The procedure to calculate the clearance needed to satisfy these conditions can best be illustrated by an example:

**Conditions:**
- patient mass: $M = 70$ kg
- toxin accumulation rate: $G = 1.8 \text{ mg}\%/\text{h (urea)}$
- maximum permissible level: $C_i = 150$ mg%
- desired schedule: $T = 48$ hr, $t = 4$ hr

The value of the 'patient number' $N_p$ will in most cases fall between 0 and 0.1. To start the calculation the value of $N_p = 0.05$ is estimated. The 'schedule number' $N_s$ can then be calculated:

$$N_s = G(T-t)/C_i(1-N_p) = 1.8(48-4)/[(1-0.05) \times 150] = 0.56.$$  

Using the right-hand scale in Figure 2, pick off 0.56 and draw a line parallel to the $N_D$ axis until it intersects with $N_p = 0$. The corresponding value of $N_D$ is read from the graph, i.e.

$$N_D = 0.83 = Kt/0.6M = K \times 4/(0.6 \times 70)$$

from which the necessary clearance can be calculated:

$$K = 8.72 \text{l/h} \approx 145 \text{ ml/min}$$

The value of $N_p$ can now be calculated since $K$ is known:

$$N_p = 0.6MG/KC_i = 0.6 \times 70 \times 1.8/(8.72 \times 150) = 0.058$$

This value of $N_p$ is so close to the assumed value that no correction is called for. If a large discrepancy should occur, the calculated value of $N_p$ is used to calculate a new value of $N_s$ and the procedure is repeated until the calculated $N_p$ and the assumed $N_p$ are equal. One iteration is usually sufficient.

The post-dialysis concentration can now be found by following the line for $N_D = 0.83$ until it intersects with $N_p = 0.058$ (previously calculated) and reading off the corresponding value of $C_t/C_i$, in this example:

$$C_t/C_i = 0.47 \text{ or } C_t = 150, 47 \approx 70 \text{ mg}\%$$

The week may be divided into two 48 hr and one 72 hr periods. When the patient comes in after the 72 hr period the higher than usual concentration level will have to be brought down to the same level as calculated earlier (70 mg% in our example, Figure 1c). Otherwise the concentration will slowly rise over a long period of time. In the above example, the concentration after the 72 hr will be

$$C_i = C_t + G(T-t) = 70 + 1.8(72-4) \approx 192 \text{ mg%}$$
This has to be brought down to 70 mg\% during the treatment, i.e.:

$$\frac{C_f}{C_i} = \frac{70}{192} = 0.364 \approx 0.36$$

If the same dialyser and flow rates are being used as for 48 hr intervals, $N_p$ can be calculated:

$$N_p = 0.6 MG/KC_i = 0.6 \times 70 \times 1.8/(8.72 \times 192) = 0.045.$$  

The necessary treatment time for the third day of the week (the day following 72 hr off treatment) can be found from the value of $N_D$ from the graph by following $C_f/C_i = 0.36$ until it intersects $N_p = 0.045$ and reading off the corresponding value of $N_D$. In the example this value is:

$$N_D = 1.06 = K \times t/0.6M = 8.72 \times t/(0.6 \times 70),$$

or solved for $t$:

$$t = 5.1 \text{ hr or rounded off, } t = 5 \text{ hr.}$$

The patient schedule is thus 3 times weekly 4 hr, 4 hr and 5 hr respectively with a clearance of 145 ml/min. Figure 1c shows how the blood concentration varies with time.

The nomogram can be used in exactly the same way for all molecular sizes.

Low blood flow rates resulting from fistula or shunt problems will lead to an extension of treatment time. Returning to Figure 2 it is seen that $C_f/C_i$ will stay constant (i.e. the value will remain as previously calculated) if only $N_D$ stays constant. (There will be a slight correction in $N_p$ as the clearance also enters into $N_p$. This correction is in most cases so small, however, that it can be neglected.) For $N_D$ to remain the same, the product $K \times t$ must remain constant, i.e. the time must be increased by the same percentage that the clearance is decreased.

Different patients will receive the same treatment if the 'dialysis number' $N_D = K \times t/0.6M$ stays constant from patient to patient, i.e. differences in patient size must be compensated for.

Clinical Material

We have been using the Norwegian plate dialyser system (Nycotron) with a large degree of flexibility as it can be built as a 1-, 2-, 3-, 4-, and 6-layer unit giving 2,500−15,000 cm² of surface area with a volume of 35−40 ml/layer. Table I shows some characteristic data in the dialyser used (Grimsrud et al, 1972, and Widerøe et al, 1974).

Seven patients were treated according to the scheme presented. They were first observed during a conventional standard haemodialysis program for a mean duration of 10.1 months (7 to 14 months). The dialysis schedules were 24 to 30 hr (mean 27 hr) twice or three times weekly.

Later on they were observed during individually calculated short-time
TABLE I. Solute Clearance of L.G.II—L.G.VI (0.50–1.5 m²) and Gambro Lundia Nova 17 μ

<table>
<thead>
<tr>
<th>Dialyser</th>
<th>Membrane area (m²)</th>
<th>Urea (mw 60) clearance</th>
<th>Vitamin B₁₂ (mw 1350) clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.G.II</td>
<td>0.5</td>
<td>95</td>
<td>11</td>
</tr>
<tr>
<td>L.G.III</td>
<td>0.75</td>
<td>117</td>
<td>15</td>
</tr>
<tr>
<td>L.G.IV</td>
<td>1.0</td>
<td>132</td>
<td>26</td>
</tr>
<tr>
<td>L.G.VI</td>
<td>1.5</td>
<td>152</td>
<td>42</td>
</tr>
<tr>
<td>Lundia</td>
<td>1.0</td>
<td>120</td>
<td>21</td>
</tr>
</tbody>
</table>

Q_B (Blood flow): 200 ml/min
Q_D (Dialysate flow): 500 ml/min

programmes for a mean duration of 6.3 months (4 to 11 months), using the previously described criteria. Urea, creatinine and vitamin B₁₂ were used as typical molecules.

Motor nerve conduction velocities (MNCV), haematocrit (HCT) and transferrin as total iron binding capacity (TIBC) were measured routinely. Blood pressure, and complications such as headache, vomiting, cramps and hypotension were compared during the two periods.

RESULTS

Table II summarises the results from the two periods. Urea and creatinine values are means of 10 measurements. The blood pressures are means of 5 pre- and 5 post-dialysis values. The calculated needs of treatment time and dialyser clearance for urea varied depending on patient weight and accumulation rate between 11.5 and 14 hr (mean 13.5 hr) and 145–180 ml/min (mean 155 ml/min) respectively. The corresponding blood flows were 250–300 ml/min (mean 275 ml/min). The membrane area was increased from an average of 0.85 m² in the standard programme to 1.25 m² for the short-time programme. The values for the two programmes show good agreement and indicate that the mathematical model used is adequate for this purpose. The variation in the accumulation rate for urea was 1.6 to 2.2 mg%/hr (mean 1.9 mg%/hr). In all instances we found calculated treatment time limited by the removal of urea and not by the removal of creatinine or vitamin B₁₂.

HCT did not change (mean 23% in both periods) and the mean values of TIBC were 278 mg% in the first and 284 mg% in the second period. MNCV was unchanged and normal throughout both periods (46.4 to 70.8 m/sec at the end of the observation).

Table III shows that hypotension and cramps in the lower limbs are more frequent in the short-time programme. But signs of osmotic disequilibrium with
### TABLE II. Calculated Short-time Dialysis Relative to Standard Protocol in 7 Patients: Urea, Creatinine and Blood Pressure

<table>
<thead>
<tr>
<th>Patient</th>
<th>Weight (kg)</th>
<th>Schedule (hr/week)</th>
<th>Membrane area (m²)</th>
<th>Urea (mg/100 ml)</th>
<th>Creatinine (mg/100 ml)</th>
<th>Blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G* (mg%/hr)</td>
<td></td>
<td></td>
<td>on/off</td>
<td>on/off/off</td>
<td>average</td>
</tr>
<tr>
<td>D.W</td>
<td>78</td>
<td>24</td>
<td>0.75 (L.G.III)</td>
<td>178 52</td>
<td>18.7 7.4</td>
<td>13.1 11.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.5</td>
<td>1.5 (L.G.VI)</td>
<td>158 70</td>
<td>16.0 6.0</td>
<td>11.4 11.0</td>
</tr>
<tr>
<td>A.L.</td>
<td>77</td>
<td>30</td>
<td>0.75 (L.G.III)</td>
<td>164 57</td>
<td>16.7 7.2</td>
<td>11.0 12.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.5</td>
<td>1.5 (L.G.VI)</td>
<td>156 74</td>
<td>14.5 7.4</td>
<td>11.5 11.0</td>
</tr>
<tr>
<td>G.B</td>
<td>51</td>
<td>24</td>
<td>1.0 (Lundia)</td>
<td>188 32</td>
<td>16.3 4.5</td>
<td>11.0 10.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.5</td>
<td>1.0 (L.G.IV)</td>
<td>186 70</td>
<td>18.2 8.8</td>
<td>12.8 13.5</td>
</tr>
<tr>
<td>E.H</td>
<td>65</td>
<td>24</td>
<td>1.0 (Lundia)</td>
<td>186 47</td>
<td>16.6 6.0</td>
<td>11.7 11.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
<td>1.0 (L.G.IV)</td>
<td>174 62</td>
<td>14.4 5.8</td>
<td>11.8 10.1</td>
</tr>
<tr>
<td>J.H.</td>
<td>60</td>
<td>27</td>
<td>1.0 (Lundia)</td>
<td>162 45</td>
<td>11.2 4.1</td>
<td>10.3 7.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>1.0 (L.G.IV)</td>
<td>158 73</td>
<td>11.8 5.9</td>
<td>11.5 8.9</td>
</tr>
<tr>
<td>P.J.</td>
<td>58</td>
<td>27</td>
<td>1.0 (Lundia)</td>
<td>169 59</td>
<td>14.3 5.9</td>
<td>11.4 10.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>1.0 (L.G.IV)</td>
<td>146 56</td>
<td>13.4 4.0</td>
<td>10.1 8.7</td>
</tr>
<tr>
<td>O.K.</td>
<td>70</td>
<td>30</td>
<td>1.0 (Lundia)</td>
<td>147 52</td>
<td>12.0 5.4</td>
<td>10.0 8.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>1.5 (L.G.VI)</td>
<td>148 39</td>
<td>12.1 4.9</td>
<td>9.4 8.5</td>
</tr>
</tbody>
</table>

- $Q_B$: Standard programme – mean 160 ml/min
- $Q_B$: Short-time programme – mean 275 ml/min
- $K$: Short-time programme – mean 155 ml/min
- $Q_D$: Unchanged 500 ml/min
- Observation standard programme – mean 10.1 months
- Observation short-time programme – mean 6.3 months
- *Urea accumulation rate – mean 1.9 mg%/hr
TABLE III. Calculated Short-time Dialysis Relative to Standard Protocol in 7 Patients: Hypotension, Cramps in Lower Limbs and Headache or Vomiting.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Standard (750 dialysis)</th>
<th>Short-time (550 dialysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>4%</td>
<td>11%</td>
</tr>
<tr>
<td>Cramps lower limbs</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Headache or vomiting</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

headache and vomiting were not increased.

All patients preferred the short-time schedule.

DISCUSSION

The one-pool model simulation is adequate in determining the dialysis schedules necessary for individual dialysis treatments, as witnessed by the agreement between calculated and measured concentration values.

There is conflict in the literature on the concentration of middle molecules required to produce neuropathy between those who find a relationship (Christopher et al 1971; Ginn et al, 1971; Millora et al, 1972) and those who do not (Cambi et al, 1973; Kjellstrand et al, 1973). The disagreement may be due to variability or absence of controls (Ginn et al, 1971; Kjellstrand et al, 1973). Without control the value of neuropathy as sensitive indication of success or failure is doubtful (Cambi et al, 1973; Kjellstrand et al, 1973).

In the present programme the patients are their own controls. This probably eliminates the influence of some of the variables.

The variation of accumulation rate (1.6 to 2.2 mg%/hr) (see Table II) indicates some variation in protein intake and metabolism and must be compensated for in the individual treatment schedules.

Note that it is the product (clearance x time) that determines whether a single patient receives equal treatments with varying treatment schedules. The (clearance x time) concept does not have any limitations on it as to molecular sizes or influence of different types of dialysers.

All our clinical parameters indicate an equivalent treatment in each period. The MNCV measurements were all normal at the end of this observation, in agreement with Kjellstrand et al, (1973).

It seems difficult to go below 10 to 12 hr/week, because of complications caused by vigorous ultrafiltration with cramps and hypotension (Table III). Other limiting factors may be the increased fall in pH of the CSF and the increased accumulation of 'idiogenic osmoles' resulting in brain oedema in too-rapid haemodialysis (Arieff et al, 1973).
Our experience is that the method is practical enough for clinical use. The nomogram (Figure 2) has been in use in our department for 18 months and is well adapted to the clinical routine. The methods described have made possible regulation of our treatment schedules with only small time variation by adjusting dialyser clearance, thus greatly increasing the efficiency of the dialysis unit. Dialysis time has been reduced by half, lessening the load on the patient with, so far, no detrimental effects.

References

Babb, A L, Popovich, R P, Christopher, T G and Scribner, B H (1971) Transactions, American Society for Artificial Internal Organs, 17, 81
Babb, A L, Farell, P C, Uvell, D A and Scribner, B H (1972) Transactions, American Society for Artificial Internal Organs, 18, 98
Bell, R L, Curtis, F K and Babb, A L (1965) Transactions, American Society for Artificial Internal Organs, 11, 183
Edson, H, Keen, M and Gotch, F (1972) Transactions, American Society for Artificial Internal Organs, 18, 113
Grimsrud, L, Smeby, L, Berg, K J and Widerøe, T - E (1972) Transactions, American Society for Artificial Internal Organs, 18, 131
Kjellstrand, C M, Peterson, R J, Evans, R L, Shideman, J R, von Hartitzsch, B and Buselmeier, T J (1973) Transactions, American Society for Artificial Internal Organs, 19, 325
Open Discussion

S SHALDON (France) Is your assumption that you are dealing with a single pool system still justified, particularly since creatinine is not equally distributed within the body? It is even more likely that large, and protein bound molecules are not treatable by a one pool mathematical model. Would a 3 pool system equation influence your calculations in any way?

WIDERØE We have tried to calculate our programmes using a 2 pool system for solutes, such as urea, creatinine and vitamin B₁₂ and the difference in the computed values compared with those in the one pool model is small and not so big as to make it necessary to use the more complicated 2 pool system.

L MIGONE (Italy) In your study you try to compare your results with an ideal standard treatment, but what is the standard?

WIDERØE The objective of this study was to compare one treatment with another, for which there is years of experience, and to try to calculate how much treatment is necessary using shorter dialysis hours. The value of the dimensionless system is that it can be used to calculate the schedule you want.