Short Time Personalised Dialysis: Good Results in Spite of High Levels of Small and Middle Molecules

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Summary

After almost two years of experience with 43 patients we believe that a short (3 x 4, 3 x 3 hr/week) personalised dialysis is a safe treatment that allows a high survival rate and a good rehabilitation of patients.

Pre-dialysis levels of small and middle molecules, the latter only calculated, did not correlate with 5 typical uraemic parameters.

Some patients, who formerly experienced standard dialysis, are now equally well or better, without evidence of increasing toxicity, in spite of their higher pre-dialysis levels of small and especially of middle molecules.

Introduction

Recent contributions lead us to believe that it is possible to shorten dialysis time safely (Orrell et al, 1971; Cambi et al, 1972 and 1973; Maiorca et al, 1973; Castellani et al, 1973).

These studies conflict, apparently, with the ‘middle molecule (MM) hypothesis’ which suggests that uraemic toxicity, mainly neuropathy, is determined by a blood accumulation of molecules ranged from 300—2000 mw (Babb et al, 1972).

However, as pointed out by Kjellstrand et al (1972) nearly all the above studies do not quantify the degree of change in MM concentrations. Thus it is impossible to say in such schedules how high the MM level actually was.

In this paper we report our experience of almost two years with short-time dialysis and we compare in our patients some clinical and laboratory data with pre-dialysis levels of two, measured, small molecules (urea, creatinine) and of a calculated middle molecule, 1355 mw.
PATIENTS AND METHODS

In November, 1972, the dialysis schedule of our centre was changed, from Kii1 standard 3 x 9 hr/week to a shorter one (3 x 5, 3 x 4 hr/week) with Gambro dialysers. Preliminary reports of our results have already been published (Maiorca et al, 1973; Castellani et al, 1973).

In this paper, 43 patients, on short-time dialysis for at least 6 months, are analysed: 36 of them, unselected, have been on 3 x 4 hr/week for 6 to 17 months (23 were formerly on 3 x 5 hr/week for 6 to 12 months); 7 patients, selected for their inter-dialysis stability have been on 3 x 3 hr/week dialysis for at least 5 months after having 3 x 4 hr/week dialysis for 6 to 12 months.

The average dialysis time is 36 months (range 8 to 100); mean age is 43 (range 19 to 61), mean weight 60.3 (43.9 to 84.4).

There are 19 uric patients, 24 with a residual kidney function and a mean creatinine clearance of 1.63 ml/min (0.22 to 4.70).

Dialysis schedules were as follows: 25 patients, 10 anuric (A) and 15 with some residual kidney function (RKF) were dialysed with a Gambro Nova dialyser, 13.5 μ, 3 x 4 hr/week, 3 patients (2 A, 1 RKF) with the same dialyser for 3 x 3 hr/week; 7 patients (2 A, 6 RKF) with Gambro Nova 17 μ, 3 x 4 hr/week, 1 patient (RKF) for 3 x 3 hr/week with the same dialyser; 4 patients (A) were dialysed with a Cordis Dow 4 HFAK for 3 x 4 hr/week, 3 patients (2 A, 1 RKF) with this dialyser for 3 x 3 hr/week.

Extracorporeal blood flow was about 300 ml/min, and was measured weekly using the bubble transit-time method. Dialysate flow was 500 ml/min.

Personalisation of dialysate was obtained with, different potassium (2, 1, 0.5 and 0 mEq/l), acetate (43, 40, 38, 35 and 32 mEq/l) and calcium (4, 3.2 mEq/l).

All our patients were on a suggested diet, the content of which was examined periodically.

In 30 random patients, the average dietary composition per day was: calories 36.1 ± 13/kg body weight, proteins 1.42 ± 0.5 g/kg, potassium 1700 ± 467 mg, phosphorus 1117 ± 368 mg, calcium 624 ± 324 mg.

Standard medication consisted of vitamin tablets, aluminium hydroxide (2–5 g/day) and intravenous iron (2–2.5 g/year). No patient had blood transfusion, or binephrectomy. Only 5 patients are receiving a mild antihypertensive treatment (propranolol).

Predialysis levels of small molecules (urea, creatinine) were determined after week-ends.

Calculation of predialysis levels (Cmax) of middle molecules (MM) was made in each case, according to Kjellstrand et al (1972), applying equation 3 for anuric patients and equation 4 for patients with residual kidney function.

Vitamin B12 (mw 1355) was used as an example of this class of molecule. When possible, we have used clearance values already reported in the literature, in order to permit comparison with clinical results of other authors.
B₁₂ clearance values used in calculation are those determined by Babb et al (1972) for Kiil Standard, Cordis Dow 3 and Minikiil dialysers, by Von Hartitzsch et al (1973) for Gambro Lundia and Cordis Dow 4 dialysers, and by ourselves for Gambro Nova 13.5 μ (24 ml/m²). For Gambro Nova 17 μ, B₁₂ clearance was calculated, applying the formula proposed by Von Hartitzsch et al (1973).

The MM 1355 mw Cₘₐₓ are expressed in this paper as arbitrary units, or as percentage of the Cₘₐₓ value obtained in an anuric patient of the same weight on 3 x 9 hr/week standard Kiil dialysis.

Values obtained as a percentage of Standard Kiil Cₘₐₓ are very similar to those obtained by calculating them with equation 9 of Babb et al (1972).

Calculation of MM 1355 mw Cₘₐₓ of toxic schedule of Ginn et al (1971), (assuming a 60 kg anuric man dialysed with a Minikiil dialyser, 3 x 7 hr/week) gave a value of 204, probably a toxic level for peripheral nerves.

An MM Cₘₐₓ of 165 is taken as a 'safe limit', after calculation of the predialysis MM level reached in a schedule of 3 x 2.5 hr/week dialysis with three Cordis Dow model 3 HFAK in series.

Blood calcium, phosphorus, triglycerides and glucose were measured with standard methods. Haematocrit was measured every week, after dialysis.

Intravenous glucose tolerance test (IVGTT) was performed 44 hr after a dialysis; evaluation of the test was made calculating the Conard ‘K’ (Conard, 1965).

Bleeding time (Ivy-time) was determined according to Mielke et al (1969).

Motor nerve conduction velocity (MNCV) was measured every two months, by the same operator under standard conditions.

For each dialysis patient 62 clinical and technical data were collected for subsequent computer analysis (3 IBM 24K system).

RESULTS

The post week-end predialytic blood levels of urea and creatinine were usually over the 'safe limit' of De Palma et al (1972), particularly in the case of creatinine.

Many patients have high calculated levels of middle molecules of 1355 mw and ten of them have levels considered unsafe by Babb (1972), and 6 anuric patients have levels higher than described as 'toxic' by Ginn et al (1971).

Our calculation of middle molecule levels gave a value of 204, possibly responsible for the onset of neuropathy.

Blood pH, K⁺, Ca²⁺, PO₄ were acceptable in our patients even after a maximum interval between dialysis, as was mean blood pressure. Five of our patients required hypotensives.

Control of dry weight was good as shown by comparison with Revines experience (Castellani et al 1974).

There was no increase in vomiting, a reduction in syncopal attacks and a
small increase in cramps.

There was no difference between anuric and residual kidney function patients in this respect, probably due to personalisation of dialysis.

Creatinine was 12% higher on average in anuric patients. There was a major calculated increase of 100% in middle molecules in anuric patients, but haematocrit, body weight, serum albumin, MNCV, IVGTT, triglycerides and Ivy-time were the same in both groups.

Eleven patients formerly dialysed for 6 to 24 months with a standard Kiil, $3 \times 9$ hr/week, were changed first to $3 \times 5$ hr/week Gambro Lundia dialysis for 7 to 11 months and subsequently, for 12 to 17 months, to a $3 \times 4$ hr/week Gambro Nova 13.5 µ or Dow Cordis 4 HFAK dialysis.

When switched from the first schedule to the second one, they had a significant increase in predialysis urea (16%) and creatinine (47%) and a marked calculated MM increase, but no change of haematocrit and body weight, whereas serum albumin increased and ulnar nerve conduction velocity improved.

On the third schedule there was no change in the recorded parameters.

Statistical comparison of the incidence of 9 signs or symptoms, collected for 2 months after 6 to 24 months of standard and 24 months of short-time ($3 \times 5$ plus $3 \times 4$ hr/week) dialysis, showed no difference between the two schedules for 8 patients. Dyspepsia however had a reduced incidence, from 2.4 to 0% in short-time dialysis.

In 10 patients who were on a very short-time schedule ($3 \times 3$ hr/week) or were dialysed inefficiently with regard to middle molecules (Cordis Dow 4 HFAK) high levels of middle molecules were calculated, considered ‘unsafe’ by Babb (1972).

Eight of 10 patients with ‘unsafe’ levels of middle molecules had previously had a comparable period of ‘safe’ dialysis, ($3 \times 4$ hr/week) with a dialyser (Gambro N. 13, 5 µ) considered more effective for middle molecules.

‘Unsafe’ dialysis was accompanied by a large increase in calculated middle molecules, whereas urea remained unchanged, and creatinine rose slightly (9%).

Notwithstanding a three-fold calculated middle molecule increase, haematocrit, body weight, serum albumin, IVGTT, triglycerides, peroneal and ulnar conduction velocity, paresthesia and Ivy-time did not change. The restless-leg syndrome improved significantly.

There was no correlation between clinical parameters and urea or creatinine (Table I).

Equally, there was no correlation between middle molecule level (as arbitrary units or as concentration increase relative to the level obtained with a $3 \times 9$ hr/week Standard Kiil dialysis) and the same parameters (Table II). Thus the clinical parameters examined were independent of small and middle molecules (calculated) in our patients.

Figure 1 shows that the survival rates in our centre did not differ between the traditional schedule and short-time dialysis, and were good in both cases.
TABLE I. Relationship Between Small Molecules $C_{\text{max}}$ and Some Parameters of Uraemia

<table>
<thead>
<tr>
<th>$X$</th>
<th>$Y$</th>
<th>number of cases</th>
<th>$r$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREATININE</td>
<td>Peroneal nerve cond vel</td>
<td>42</td>
<td>-0.2015</td>
<td>&gt; 0.1</td>
</tr>
<tr>
<td></td>
<td>Ht</td>
<td>42</td>
<td>0.1567</td>
<td>&gt; 0.1</td>
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<tr>
<td></td>
<td>Ivy-time</td>
<td>43</td>
<td>0.0475</td>
<td>&gt; 0.1</td>
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<tr>
<td></td>
<td>Serum triglycerides</td>
<td>28</td>
<td>0.3489</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td></td>
<td>IVGTT</td>
<td>21</td>
<td>0.0204</td>
<td>&gt; 0.1</td>
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<tr>
<td>UREA</td>
<td>Peroneal nerve cond vel</td>
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<td>-0.0849</td>
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<td>Ht</td>
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<td>-0.1038</td>
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<tr>
<td></td>
<td>Ivy-time</td>
<td>43</td>
<td>0.2078</td>
<td>&gt; 0.1</td>
</tr>
<tr>
<td></td>
<td>Serum triglycerides</td>
<td>28</td>
<td>0.1178</td>
<td>&gt; 0.1</td>
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<tr>
<td></td>
<td>IVGTT</td>
<td>21</td>
<td>-0.2975</td>
<td>&gt; 0.1</td>
</tr>
</tbody>
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TABLE II. Relationship Between Middle Molecules $C_{\text{max}}$ and Some Parameters of Uraemia

<table>
<thead>
<tr>
<th>$X$</th>
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<th>$p$</th>
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<tbody>
<tr>
<td>MIDDLE MOLECULES</td>
<td>Peroneal nerve cond vel</td>
<td>39</td>
<td>-0.27666</td>
<td>&gt; 0.05</td>
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<tr>
<td>(arbitrary units)</td>
<td>Ht</td>
<td>40</td>
<td>-0.01200</td>
<td>&gt; 0.1</td>
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<tr>
<td></td>
<td>Ivy-time</td>
<td>40</td>
<td>0.12350</td>
<td>&gt; 0.1</td>
</tr>
<tr>
<td></td>
<td>Serum triglycerides</td>
<td>27</td>
<td>0.31659</td>
<td>&gt; 0.1</td>
</tr>
<tr>
<td></td>
<td>IVGTT</td>
<td>21</td>
<td>0.22720</td>
<td>&gt; 0.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>$X$</th>
<th>$Y$</th>
<th>number of cases</th>
<th>$r$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIDDLE MOLECULES</td>
<td>Peroneal nerve cond vel</td>
<td>39</td>
<td>-0.24300</td>
<td>&gt; 0.1</td>
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<tr>
<td>(% $C_{\text{max}}$ relative to a St. Kill 3 x 9 hr/week)</td>
<td>Ht</td>
<td>40</td>
<td>-0.03120</td>
<td>&gt; 0.1</td>
</tr>
<tr>
<td></td>
<td>Ivy-time</td>
<td>40</td>
<td>0.02000</td>
<td>&gt; 0.1</td>
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<tr>
<td></td>
<td>Serum triglycerides</td>
<td>27</td>
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<td>&gt; 0.1</td>
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<tr>
<td></td>
<td>IVGTT</td>
<td>21</td>
<td>0.24496</td>
<td>&gt; 0.1</td>
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</table>

(88% at 24 months) in both groups.

Patients’ rehabilitation is good: only five patients (12%), some aged, are unable to work, but can take care of themselves. The other 38 (88%) can work and the majority are doing so.

DISCUSSION

In our experience, a 3 x 4 hr/week dialysis with dialysers as efficient as those we used is a safe treatment for anuric patients.

Greater care is necessary over ultrafiltration, but the reduced incidence of syncope demonstrates that this is not difficult.

Personalisation of dialysate and care with phosphate binders are particularly
important. Patients did not complain of more limitations in their life than when they were on longer dialysis. In fact they always claimed to feel better.

A shorter schedule, 3 x 3 hr/week, should be reserved for patients with a residual diuresis or with good control of their food and water intake.

Phosphate level is the main limitation on short dialysis; however, we have no evidence that short-time dialysis worsens uraemic osteopathy in our patients.

In this study we found no correlation between clinical and laboratory data characteristic of uraemia and levels of small and calculated middle molecules.

This lack of correlation between clinical parameters and molecular size suggests that uraemic toxins, do not reach toxic predialysis levels even in very short dialysis.

Thus a 45 to 65% reduction of dialysis time does not, in our experience, worsen the patients' state.

Finally in discussing the hypothetical toxicity of middle molecules and remembering the limits imposed by indirect measurements, it is reasonable to ask whether an apparent 3-fold incidence in middle molecules in the face of lack of clinical evidence of toxicity is consistent with the ‘middle molecule hypothesis’.

References

Babb, A L (1972) Proceedings Clinical Dialysis and Transplant Forum, 2, 152 and 154
Cambi, V, Savazzi, G, Arisi, L, Buzio, G, Dall’Aglio, P, Rossi, E and Migone, L (1973) Proceedings of the European Dialysis and Transplant Association,
Open Discussion

I REITINGER (GFR) Have you compared your middle molecule results with the results of Fürst and Bergström and how did you measure middle molecules?

MAIORCA We did not measure predialysis middle molecule levels. We only calculated them because this is, so far, the only useful method for clinical purposes. So, we could not compare our predialysis level with the results of the above authors.

P KRAMER (GFR) What was the frequency of pericarditis in your patients on short dialysis?

MAIORCA We have had only one case of pericarditis in our centre in four years, and it began just before starting haemodialysis.