Dialysis Schedule and Peripheral Neuropathy

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For several years peripheral neuropathy has been considered one of the most disturbing problems in chronic haemodialysis and the only way to prevent worsening of the disease appeared to be a more vigorous dialysis treatment (Tenckhoff et al., 1965).

The empirical correlation between prolonged dialysis schedule and lack of neuropathy has never been well understood, and any attempt to quantify the phenomenon (Dobbelstein et al., 1972) is in contradiction with several observations: for instance, the lack of neuropathy in peritoneal dialysis (Tenckhoff & Curtis, 1970) and low flow haemodialysis patients (Cambi et al., 1972), treated as in standard haemodialysis but at a lower removal of small molecules; the presence of neuropathy in some patients also treated with the 24-30 hours standard haemodialysis schedule, twice or thrice weekly and the worsening of peripheral neuropathy after the beginning of chronic haemodialysis.

According to some experimental data supporting the middle molecules hypothesis (Scribner et al., 1972; Ginn et al., 1971; Funck-Brentano et al., 1972) there should be a correlation between peripheral neuropathy and accumulation of middle molecules in uraemic tissue.

The purposes of the present report are:

(1) To assess the minimum dialysis requirement compatible with normal well being and lack of neuropathy (Protocol 1).

(2) To check if an increased removal of middle molecules can improve the status of the peroneal nerve if abnormal, at least on a motor nerve conduction velocity basis (Protocol 2).

(3) To assess the influence of a very reduced removal of molecules of any size, when ultrafiltration, acid-base, and potassium are correctly maintained (Protocol 3).
PROTOCOL AND METHODS

The progressive reduction of the dialysis schedule started in November 1971, and the preliminary results were published in the last Proceedings (Cambi et al, 1972).

The present population was divided into three groups (Table I).

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients</th>
<th>Weekly schedule (hr)</th>
<th>Surface area (sq.m)</th>
<th>Q_B</th>
<th>Q_D</th>
<th>Period of observation (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>50</td>
<td>10.5-12</td>
<td>1</td>
<td>250-300</td>
<td>500</td>
<td>up to 11-12</td>
</tr>
<tr>
<td>Group 2</td>
<td>4</td>
<td>10.5</td>
<td>1.68-2.0</td>
<td>250-400</td>
<td>500</td>
<td>4</td>
</tr>
<tr>
<td>Group 3</td>
<td>3</td>
<td>5.15</td>
<td>1.5</td>
<td>500</td>
<td>500</td>
<td>40 days</td>
</tr>
</tbody>
</table>

**Group 1**

Dialysis schedule: 3 hours every other day (EOD) or 4 hours thrice weekly. Blood flow in ml/min (Q_B), 250 or more. Dialysate flow in ml/min (Q_D), 500.

Surface area of the dialyser: 1 sq.m.

Dialysers: UF 100, UF 2, Gambro Lundia, Dasco SP 75.

Dialysate composition (mEq/l) Acetate 38, Na 135, K 0-1.2, Calcium 4, Magnesium 1.5, Chloride 102.5-104.5.

Diet: Protein content 1.0-1.4 g/kg body weight, mostly (2/3) high biological value; calories 2500-3500.

Age of the patients: 21-62 years; mean age 39.4. Number of patients: 50

Post-dialysis weight: 58.4 + 8.2 kg (47.5-72).

Period of observation: 11-12 months.

**Group 2**

Dialysis schedule: 3 hours EOD.

Q_B 250-400; Q_D 500.

Surface area of the dialysers: 1.68-2.0 sq.m.

Dialysers: 1 EX03 x 2 in parallel, 1 Gambro Lundia x 2 in parallel, UF 1.5 Travenol.

Dialysate composition: as above.

Diet: as above.

Age of patients: see Table II. Number of patients: 4.

Post-dialysis weight: see Table II.

Period of observation: 4 months.

**Group 3**

Dialysis schedule: 90 minutes EOD (5.15 hours weekly).
Table II.

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Weight (kg)</th>
<th>BP (mmHg)</th>
<th>K (mEq/l)</th>
<th>P (mg%)</th>
<th>Uric acid (mg%)</th>
<th>Urea</th>
<th>Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative data referred to the period of observation</td>
<td>58.4±8.2</td>
<td>148±25/90±14</td>
<td>5.02±0.7</td>
<td>5.92±1.89</td>
<td>8.94±1.38</td>
<td>see Table III</td>
<td>see Table III</td>
</tr>
</tbody>
</table>

**Group 2**

| AL-Male, age 24 anuric | Before    | 68.3±0.4        | 157±16/98±9  | 5.8±0.8   | 7.7±0.7         | 7.8±1.3 | 206±18     | 16.7±1.5   |
| BM-Male, age 30        | Before    | 66.3±0.2        | 175±11/101±10| 5.5±1.0   | 7.6±0.9         | 13.0±0.6 | 319±46     | 14.1±0.7   |
| SE-Male, age 31        | Before    | 64.8±0.7        | 161±17/111±13| 5.3±0.3   | 7.1±1.2         | 11.5±1.3 | 264±48     | 17.4±1.7   |
| GG-Female, age 62      | Before    | 52.8±0.3        | 171±14/96±6  | 6.3±0.8   | 6.8±1.8         | 8.0±0.7  | 186±17     | 12.1±0.5   |

**Group 3**

| CR-Male, age 28        | Before    | 68.8±0.5        | 142±10/67±9  | 5.5±0.3   | 6.3±1.3         | 9.4±0.3  | 244±22     | 17.4±0.9   |
| FF-Female, age 44      | Before    | 51.2±0.5        | 161±12/106±4 | 6.3±0.7   | 5.9±0.9         | 8.26±1.2 | 206±47     | 12.4±1.4   |
| GR-Female, age 22 anephic | Before | 49.9±0.4       | 128±11/79±8  | 4.3±0.5   | 6.4±1.6         | 8.92±0.8 | 157±30     | 11.7±0.3   |

Before - Mean values for 6 months before the study always using 1 sq. m dialysers
After - Mean values throughout period of observation
○ P = during the period of observation phosphate binders were completely withheld
○ Post Dialysis weight

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273
\( Q_B \ 500; \ Q_D \ 500. \)
Surface area of the dialyser: 1.5 sq.m.
Dialyser: Travenol UF 1.5.
Dialysate composition: as above.
Diet: as above.
Age of the patients: see Table II. Number of patients: 3.
Post-dialysis weight: see Table II.
Period of observation: 40 days (60 dialysis runs).

MOTOR NERVE CONDUCTION VELOCITY

Motor nerve conduction velocity (MNCV) was collected with a dual-channel Hewlett Packard 1510 A electromyograph, with a variable persistence storage scope. Motor Action Potentials (MAP) recorded from ulnar and peroneal nerves were obtained with sensitivity 2mV/cm sweeptime 2ms/cm and orthodromic single stimulation with a pulse width of 200 \( \mu \) sec and variable voltage from 0 to 325 volts to obtain a supramaximal response. Routine use was made of bipolar needle electrodes.

Cumulative number of measurements of motor nerve conduction velocities: ulnar nerve 716, peroneal nerve 686.

NEUROLOGICAL TESTS

Clinical investigation included examination of peripheral reflexes and examination of the muscular trophism of the lower legs. A detailed assessment of sensory functions was not performed, both because of the objective difficulties in quantifying sensory disturbances and because the investigation regarding tingling, numbness or pain was always negative after six months of treatment.

RESULTS

Cumulative values of the patients of Group 1 are reported in Table II, together with detailed results of the patients belonging to Group 2 and Group 3.

General considerations

(a) All the dialysis population receives at least 3 g of iron per year. No blood transfusions were required. Several patients of Group 1 were treated with aluminium hydroxide: this therapy was completely withheld in Group 2 to evaluate the net effect on serum phosphates using a large surface area dialyser. A few patients of Group 1 and 2 were treated with guanethidine. One patient of Group 1 and one patient of Group 2 were treated with peroral exchange cation resins to keep serum potassium in normal limits.

(b) Complications such as uraemic pericarditis were never observed.
Table III. Dialysis time reduction

<table>
<thead>
<tr>
<th></th>
<th>Predialysis serum urea (mg%) mean ± SD</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Group 1</td>
<td>199 ± 37</td>
<td>238 ± 48</td>
</tr>
<tr>
<td>Group 2</td>
<td>244 ± 60</td>
<td>201 ± 53</td>
</tr>
<tr>
<td>Group 3</td>
<td>202 ± 43</td>
<td>227 ± 48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Predialysis serum creatinine (mg%) mean ± SD</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Group 1</td>
<td>13.3 ± 1.1</td>
<td>15.5 ± 1.7</td>
</tr>
<tr>
<td>Group 2</td>
<td>15.1 ± 2.4</td>
<td>15.2 ± 2.3</td>
</tr>
<tr>
<td>Group 3</td>
<td>13.8 ± 3.1</td>
<td>19.1 ± 3.9</td>
</tr>
</tbody>
</table>

(c) The mean predialysis values of urea and creatinine measured at the start and during the experiments are reported in Table III. The predialysis values of urea and creatinine of Group 1 do not refer to all the population but only to a restricted Group of 9 males with a creatinine clearance under 0.5 ml/min. The decision was made in order to assess practically the highest predialysis level, obtainable in a homogeneous, male population, with a highly reduced urine output.

NEUROLOGICAL TESTS ON THE LOWER LIMBS

Clinical tests

Quadriceps reflex and/or Achilles reflex, at least on one side, were absent in 11 patients (22%). In 8 patients (16%) quadriceps or Achilles reflex were diminished but present. In 3 patients out of 4 belonging to the 2nd Group, reflexes were absent or diminished with no atrophy in the legs; after 4 months it was not possible to document any improvement. Restless leg syndrome

![Figure 1. Ulnar motor nerve conduction velocity. () = number of measurements](image-url)
Figure 2. Peroneal motor nerve conduction velocity. ( ) = number of measurements

Figure 3. Peroneal motor nerve conduction velocity with different dialysis schedule in the same patients

was present in 5 patients (10%) but not correlated with MNCV in the peroneal nerve.

Four patients with profound weakness and inability to walk at the beginning of the dialysis treatment were normal after 6 months of reduced dialysis schedule (1st Group).

Motor nerve conduction velocities

Figures 1 and 2 show the frequencies of MNCV of the ulnar and peroneal nerve in the overall population compared with the MNCV of the patients on conservative treatment: in the 'conservative' Group the mean creatinine clearance is 8.6 ml/min. The highest frequency of the velocities of the
ulnar nerve is in the range of 46-50 m/sec in the dialysed group; the peroneal nerve presents the highest frequency in the range of 36-40 m/sec. In literature (Thomas et al, 1959) both values are in the normal range.

Figure 3 shows the frequencies of MNCV of the peroneal nerve in patients treated with 14.5 hr/week (coil dialysers) to 30 hr/week (Kid dialysers), versus the population dialysed no more than 12 hr/week. The comparative MNCV in patients treated with a reduced schedule, or large surface area dialysers (LSAD), or combining high efficiency and LSAD (Group 3) in order to reach a very reduced dialysis schedule, do not show any statistically significant difference (Table IV).

**Table IV. Motor nerve conduction velocities.**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Patients</th>
<th>Results</th>
<th>Period of observation (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>A</strong></td>
<td>Standard Kiil 27 hr/w versus coil 1 m² 10.5 hr/w</td>
<td>18</td>
<td>42.8±9.0</td>
</tr>
<tr>
<td></td>
<td>coil 1 m² 17.5 hr/w versus coil 1 m² 10.5 hr/w</td>
<td>9</td>
<td>38.1±7.9</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>coil 1 m² 14.5 hr/w versus coil 1 m² 10.5 hr/w</td>
<td>18</td>
<td>39.5±3.7</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>conservative treatment versus coil 1 m² 10.5 hr/w</td>
<td>5</td>
<td>37.8±5.9</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td>coil 1 m² 10.5 hr/w versus 1.7-2.0 m² dialysers 10.5 hr/w</td>
<td>4</td>
<td>32.4±7.95</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Group 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>coil 1 m² 10.5 hr/w versus coil 1.7 m² 5.15 hr/w</td>
<td>3</td>
<td>37.8±6.7</td>
<td>40 days</td>
</tr>
</tbody>
</table>

**Note**
- All protocols are still in progress
- None of the differences within each group are statistically significant

All the experiments with reduced schedules are still in progress. The 3rd Group was included in the present paper mainly to show, after 60-dialysis runs, the feasibility of such a schedule as far as control of ultrafiltration and disequilibrium syndrome; in addition, to study the influence on the peripheral nerve of rapid changes in homeostasis. The problems related to
the removal of neurotoxic substances are better faced by the patients of
Groups 1 and 2.

DISCUSSION

In spite of the fact that the uraemic picture involves any organ and system,
peripheral neuropathy, more than any other clinical sign, has always been
the practical 'marker' of the dialysis need (Pendras & Erickson, 1966).
The correlation between prolonged dialysis schedules and the improvement
or cure of neuropathy has apparently been the best confirmation of the fact.

The diagnosis of peripheral neuropathy, when the sensory involvement
is marginal or missing at all, can only be assessed by the measurement of
MNCV. According to our experience, a worsening of peripheral neuropathy
is always anticipated by a severe reduction of MNCV; on the contrary, pro-
found swinging of MNCV (also over 10 m/sec) may not be accompanied by
clinical changes.

Some clinical trials appearing in the literature seem to confirm the
hypothesis that an improved removal of those solutes which are most depen-
dent on time-area product may be beneficial involving a specific toxicity of
middle molecules. However, some of these experiments are retrospective
(Ginn et al, 1971) and, as far as MNCV, the measurements are very limited,
or conducted in a few patients (Christopher et al, 1971; Man et al, 1973;
Rosenzweig et al, 1971), and it is objectively difficult to make comparisons
with them.

A reduction of the dialysis schedule together with more frequent dialysis
runs, minimises the changes of predialysis levels of small molecules with-
out influencing too much the middle molecule level (Kjellstrand et al, 1972).
This strategy, together with very high blood flows helps to keep the homeo-
stasis of the patients constant, avoiding disequilibrium problems. Our
experiments with short and frequent dialysis and the experiments performed
in other institutions with short but not necessarily frequent dialysis (Berman,
1971), did not modify the clinical status of the patients in spite of a signifi-
cant increase in small molecule levels, but, in the meantime did not offer
any solution to the middle molecule problems, as the minimum dialysis
requirement is still unknown.

On doubling the surface area (Group 2) of the dialysers, MNCV, already
stable on low values for the previous six months, did not improve in our
patients. These results, if confirmed for a longer time, would contradict
the middle molecules hypothesis; however, a definite toxicity of middle
molecules could be excluded only by the lack of any improvement of other
metabolic parameters. An extensive study regarding this assessment is
still in progress.
It has been recently stated that a correct ultrafiltration, and diastolic blood pressure plus correct serum potassium are extremely important in preventing neuropathy (Kjellstrand et al, 1973). The studies still in course with the 3rd Group of patients will show the actual influence of high urea and creatinine concentrations obtained with this schedule over a longer period, and could help in distinguishing the influence of a correct water-saline balance in the clinical status. The aim of this strategy is to consider, within reasonable limits, urea and creatinine, and related small metabolites, important, but not essential in the genesis of uraemic toxicity.

CONCLUSIONS

The condition of the dialysis patients has changed remarkably in the last few years. Neuropathy does not seem to be correlated per se with our changes of standard dialysis schedules. On the other hand the enlarging of the surface area does not improve the MNCV of the patients. Predialysis figures continue to be often far from normal. The isolated improvement of the haematocrit could simply be related to a reduced mechanical damage of the red cells in the extracorporeal circulation (Cambi et al, 1973). The stability shown by MNCV serves only to demonstrate that changes in MNCV described in the literature are probably more influenced by other factors, infections and antibiotic therapy, poor dietary control, etc. Furthermore, if a reduced schedule does not damage MNCV, it is not possible to exclude, presently, that more efficient dialysers and identical schedules could positively influence other parameters over the long term.

The avoidance of disequilibrium shown by the patients of Group 3 is very helpful in considering these new perspectives.

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OPEN DISCUSSION

H TENCKHOFF (Seattle): I do not want to discuss middle molecules, but I should like to suggest that perhaps four months is not sufficient time to evaluate the effect of any haemodialysis regime on the improvement of neuropathy. It has been shown many times that perhaps six months or longer may be needed before the latter is seen.

CAMBI: Yes, I agree with you. Unfortunately, the detailed results are in the papers, but in two patients there is a slight decrease in neuropathy - although not statistically significant. Certainly in four months we are hardly likely to see any improvement.

A BABB (Seattle): How many of the 57 patients had some residual renal function?

CAMBI: Recently we tried to assess the function of all our patients. In the first group most patients do not have a creatinine clearance of more than 1 ml/min. In the second group we have one anuric patient and one with a creatinine clearance of less than 0.5 ml/min. In the third group we have a 70 kg man totally anuric, a girl who is anephric and a patient with a creatinine clearance of 0.8 ml/min.

BABB: We at Seattle believe that residual renal function corresponding to a creatinine clearance as low as 1 ml/min can have a profound effect on the treatment.

CAMBI: Yes, I know the Seattle point of view and that is the reason why we selected an anuric patient in the last group, and we are trying to study the patients annually.

280
C JACOBS (Paris): How do you manage to take the fluid off the patient with such short dialysis periods?

CAMBI: It depends on the educability of the patient. They have to limit their weight gain due to fluid intake, so that you do not need to remove more than 1.3 kg at a time. If the patient is not willing to respect a limited range of weight, he cannot enter this programme, but they generally agree to the reduced dialysis.

BABB: I see. Would you agree therefore that your patients are more strictly limited in fluid intake than other?

CAMBI: Yes, I do agree that the patients are more restricted. It may be that this restriction is not very agreeable to the patients, but I do feel that if the patients are not restricted in this way, they will have problems in the long term.

In conclusion I should like to say that our research is not a demonstration of the non-toxicity of middle molecules. We only suggest that the blood level of middle and small molecules - which possibly are involved in the toxicity related to the uraemic syndrome - is probably higher than previously stated, so that within certain limits we can shorten dialysis time without danger of worsening the clinical situation, even if surface area and membrane permeability are not increased. The introduction of these last two factors can perhaps further change and improve the dialysis procedure.