ASSESSING THE ADEQUACY OF DIALYSIS

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Summary

In previous work, probes of brain function (quantified EEG and cognitive performance) objectively measured clinical differences between patients with chronic renal failure before and after treatment with maintenance haemodialysis or transplantation. This study applied those measures (EEG-discriminant score; choice reaction time, CRT; continuous memory test, CMT; clinical-symptom/self-evaluation questionnaire, CSE) in a prospective experiment to determine whether our standard amount (time) of thrice weekly dialysis could be reduced without inducing some degree of clinical uraemia.

In 10 patients a 6 month experimental (E) period was preceded by a 3 month control (C1) and followed by a 3–6 month control (C2) period. During E dialysis time was reduced so that residual renal ($K_r$) plus dialyser ($K_d$) urea clearance per week per litre of patients' body water approximated 50–80 percent of the control-level of 3000ml/wk/L. In response average values of all measures worsened: EEG*, 54 percent; CRT, 2.5 percent; CMT*, 21 percent; and CSE*, 11 percent. BUN levels rose slightly, urea generation rates fell, and patients insisted that they felt better as they recorded more severe symptoms (CSE).

We conclude: (i) that $K_r + K_d = 3000$ ml/wk/L approximates a minimum level of adequate dialysis; (ii) objective measures which index the neurobehavioural syndrome of clinical uraemia detect inadequate (reduced) dialysis.

Introduction

The clinical sickness of acute or chronic progressive renal failure consists of nonspecific symptoms of concurrent agitation and depression. The fatigue, malaise, impaired attention-span, daytime drowsiness, insomnia, anorexia, nausea, myoclonus and restlessness occur early in the course in virtually all patients. As they progress these symptoms typically send patients home from work, to their doctors

*p less than .01
and ultimately to their beds. By inspection these symptoms are evidently generated or mediated by the central nervous system (CNS); and, in the absence of other diseases which might also produce them, they are among the primary, classical indications for dialysis because dialysis reverses them [1–3].

The remaining organ systems evidently respond to renal failure in a clinically different way. For example, when renal failure incites disorders in the erythron, peripheral nerves, bones, gut or skin, these disorders are usually detected by physical findings or laboratory abnormalities rather than as disabling symptoms. Moreover, these non-CNS findings and symptoms typically appear ‘late’ in the clinical course, and respond sluggishly or not at all to dialysis treatment [3].

Thus, if we wish to assess adequacy of dialysis in the treatment of patients, it seems only reasonable to seek the evidence where the action is — where dialysis has its most obvious clinical effect — i.e. in relevant indicators of patients’ dialysis-responsive disability and in the CNS generator of that disability itself. Conversely, one would hardly seek evidence for adequacy of dialysis among dialysis findings or symptoms which do not respond to dialysis.

In 1979 we published our evidence that both electroencephalographic and psychometric measures could discriminate quantitatively between patients with chronic renal failure, before and after treatment with chronic haemodialysis, and successful renal transplantation [2]. The three EEG measures (power spectrum, visual evoked response and photic driving response) and the three psychometric measures (continuous memory test, choice reaction time and continuous performance test) responded similarly to ‘undialysed’ renal failure to maintenance dialysis and to transplantation [4]. In short, we looked where the action should be and discovered quantitative and congruent changes in the brain’s electrical activity and cognitive function, which matched the expected clinical differences in the patients. Therefore, we were encouraged to use these quantitative neurobehavioural measures in assessing the adequacy of dialysis.

In the present study, the measures were used as dependent-variable end points to assess the effect of a one-third reduction of the independent variable: the amount of combined dialyser and residual renal urea clearance.

Method

Patients

Ten patients aged 25–56 years with end stage chronic renal failure entered the study. Renal diagnoses included hypertensive nephrosclerosis (7), lupus nephritis (1), renal artery stenosis with hypoplastic contralateral kidney (1) and polycystic kidney (1). Each patient had been treated by means of maintenance haemodialysis for at least six months prior to beginning the study. One patient transferred to another dialysis unit prior to the second control period. Her data are accordingly excluded from the analysis although the results in the initial control and experimental period are consistent with those of the remaining patients.

Experimental design

Table I reveals the switchback design in which a six-month experimental period (E) was bracketed by an initial three-month, (C₁), and a final three to six months
TABLE I. Experimental design

<table>
<thead>
<tr>
<th></th>
<th>Control-1</th>
<th>Experimental</th>
<th>Control-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>3 months</td>
<td>6 months</td>
<td>3–6 months</td>
</tr>
<tr>
<td>Number of patients</td>
<td>10</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>

**Independent variable:**

<table>
<thead>
<tr>
<th>$K_T$ Urea, (ml/wk/L)</th>
<th><strong>Design:</strong></th>
<th><strong>Actual:</strong></th>
<th><strong>Range:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3000</td>
<td>3046</td>
<td>2885–3256</td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>2168</td>
<td>1723–2456</td>
</tr>
<tr>
<td></td>
<td>3000</td>
<td>3017</td>
<td>2725–3522</td>
</tr>
</tbody>
</table>

**Intermediate variables:**

Chemical; 'Urea appearance rate'

**Dependent variables:**

- EEG: Discriminant score; Power spectrum
- Psychometric: CRT: Choice reaction time
- CMT: Continuous memory test
- CSE: Clinical self-evaluation score

($C_2$) control period for each patient.

The *independent variable* was the amount of dialysis as measured by the $K_T$ urea, i.e. the sum of the dialyser urea clearance plus the residual renal urea clearance in millilitres per week for each patient, divided by the patient’s estimated body water in litres (urea space). The latter step serves to equalise the amount of urea clearance among patients of different sizes and sexes. The control level was set at 3000ml/wk/L which is arithmetically equal to 10 percent of ‘the normal glomerular filtration rate' (125ml/min) in a 70kg man with a body water volume of 42L.

$K_T$ urea was reduced to a target level of 2000ml/wk/L during the experimental period by reducing the dialysis time appropriately. However, the actual average value of $K_T$ urea (Table I) was individually altered when shortages of dialysers forced a change in dialyser model, when fistulae failed to support prescribed blood flows, or when dialysis times were changed from prescribed levels by patients’ transportation arrangements. The actual dialysis parameters were recorded at each dialysis session, however, and the computed dialyser clearances contributed to the averages for each patient and to these averages for the group.

Plasma solute composition, dietary intakes and urea 'appearance rates' were allowed to fluctuate as measured or computed *intermediate variables*. This designation implies that the known, conventionally measured solutes are probably irrelevant to the principal outcome effect of dialysis upon the neurobehavioural (*dependent variable*) disabilities of renal failure.

**Chemical**

Standard autoanalyser methods were used for serum chemical determinations. Urea (nitrogen) appearance rates in mg/min were calculated at least once during each period as follows: the sum of the urea nitrogen excreted in the urine (if any)
in the interdialytic interval plus the average of post- and pre-dialysis BUN values from the two successive dialyses were multiplied by the body water volume, and this product was divided by the interdialytic interval in minutes.

Results

Figure 1 presents the principal results from the nine patients who completed all three periods of the study. The control and experimental means plus or minus standard errors of the mean are shown for the EEG discriminant score [5], the EEG power spectrum (i.e. the power associated with slow waves (3–7 Hz) as a percent of total EEG power in the occipital leads between 3–13 Hz), the choice reaction time (CRT), the continuous memory test (CMT) and the score of a clinical self-evaluation questionnaire. In all cases, 'worse' is 'up'. Means of dependent variables in periods C₁ and C₂ were not statistically different, and were therefore averaged for subsequent calculations. Compared with the average of C₁ plus C₂ values, all measures were more abnormal during the experimental period*. The change in EEG, CMT and CSE reached statistical significance at the p < 0.01 level. Though complicated by an apparent difference in C₁ and C₂ averages, the abnormal duration of the experimental CRT average from the mean of the control periods was numerically tiny and statistically insignificant. Our previously published means ± standard errors for maintenance haemodialysis patients are shown at the bottom of the figure for each measure.

The unplanned splay of individual reductions of $K_T$ urea during the experimental series prompted us to plot the dependent variable responses individually in the order of declining $K_T$ urea expressed as a percent of each patient's averaged control levels (Figure 2). Concurrent calculated $B_{12}$ clearances are similarly plotted. The changes in neurobehavioural measures are plotted in absolute values adjusted (EEG discriminant score X 10 and CRT, seconds X 10) for display on the same ordinate scale. In this sample, only the change in the EEG discriminant score (solid bars) was systematically related to the change in $K_T$ urea. That relationship is a linear regression: $\Delta$ Discriminant score = (−0.000577)$K_T$ urea + 1.5864 with $K_T$ urea expressed in ml/wk/L ($r_s = 0.88$, p < 0.01). The level of $K_T$ urea corresponding to a zero-EEG-change from control is the X-intercept, 2750 ml/wk/L.

Discussion

The following additional comments are warranted:

1 When we quantify dialysis by means of the urea marker we in no way imply that urea is toxic, i.e. is responsible for the measured neurobehavioural deficits in patients with renal failure.
2 While the regression of $\Delta$ EEG on $\Delta K_T$ urea is statistically significant in this sample, that of $\Delta$ EEG upon the change in calculated $B_{12}$ clearance is not. However, we doubt that this finding has biological significance in terms of

* In the tenth patient all measures but the CRT were also more abnormal in E than in C₁

700
Figure 2. Response of neurobehavioural measures and reductions of urea and calculated \( B_{12} \) clearances during the experimental period.
the relative toxicity of small and ‘middle’ molecules on several a priori grounds because these variables are confounded and because the sample size is small. 
3 In contrast to our earlier work, the neurobehavioural variables especially EEG and CMT are not intercorrelated in this sample.
4 The 95% confidence limits of the regression coefficient in this study cause the X-intercept of this regression to vary from 2000 to 4000 millilitres per week per litre; — a range, but not yet a precise number, by which to estimate an adequate amount of dialysis.
5 In consequence of reduced dialysis, BUN concentrations rose, but to less than predicted levels because urea appearance rates declined.
6 Patients insisted that they were doing well, preferring the shorter dialysis times during the experimental period. However, their serial responses on the clinical self-evaluation questionnaires uniformly revealed more severe symptoms.
7 We have no information concerning possible improvement in EEG or in cognitive function if total urea clearances were increased. Such studies are underway.

Conclusion

We conclude (1) that dialyser plus residual renal urea clearance at 3000ml/wk/L approximates a minimum level of adequate dialysis; (2) that neither BUN or other chemical changes nor patients’ conversations are reliable indicators of suboptimal dialysis in the ranges we examined; (3) that objective measures which index the neurobehavioural syndrome of clinical uraemia are more abnormal when dialysis is reduced; and (4) that such measures are very likely to help us choose the best modality and amount of dialysis treatment for our patients in terms of the symptomatic control which is the main object of such treatment in the first place.

Acknowledgments

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Nashville
Open Discussion

DRUEKE (Paris) You insist rightly on neurobehavioural abnormalities which occur when dialysis time is shortened too much. This could be another warning against the current tendency towards too much altering of dialysis time. However, the uraemic syndrome is not only characterised by neurobehavioural abnormalities, but also by many other abnormalities such as the degree of anaemia, cardiovascular changes, renal osteodystrophy and so on. Would you agree that you have also to take changes of all these parameters into account before concluding that there is a decrease in performance or an increase in uraemic syndrome?

TESCHAN The question points out one of the key areas of disagreement and of argument and of misconception in the field, in my view. The question really is, does dialysis replace all of the functions of the normal kidney? That is, when we do dialysis, do we really expect every abnormality of the so called total uraemic syndrome to be favourably affected? I think that Dr Merrill's opening remarks this afternoon have gone a long way to settling that question. Our view is that whether or not dialysis affects the entire uraemic syndrome depends on what you mean when you use the word. We believe that the use of the term uraemia should be discarded; that its sloppy and imprecise usage has been a major deterrent to clear thinking in the field. We believe that if we are going to use the term it needs to be very specifically defined. The area of this presentation has to do with those elements of a patient's illness which dialysis promptly and clearly reverses. That, we submit, is a neurobehavioural syndrome. There is no very good evidence, that I know of, that dialysis materially affects all the other abnormalities in all the other organ systems and therefore to attribute all those other failures to an inadequacy of dialysis is to miss the point and to confuse the issue. For this reason we believe that to look in the brain for what dialysis does is critically important. If other organ systems are also affected, this is also very interesting but still to be explored.

DI PAOLO (Chieti, Italy) Is it correct to correlate neurobehavioural dysfunction with EEG abnormalities? Errors are frequent for we know electrocortical activity is a product of influx and efflux stimuli which influence the findings.

TESCHAN Yes, regarding the correlation between electrical activity in the brain at the level of neurophysiology or at least the summation of a lot of activities (because by the way the EEG is not understood itself) and cognitive function which is a whole organism function (as is an EEG itself) requiring an entire organ and its connections to function, we have been impressed with the fact that these apparently travel together in our initial set of observations. We are disturbed by the fact that we were not able to find that congruence in the reduction of dialysis experiments here. There are serious troubles even with the EEG regression because of the confidence limits of that regression coefficient. I hope that by expanding a very limited number of patients we can come to greater precision. I think that if this audience and my colleagues
will at least grasp the notion that dialysis research is certainly possible to do in a prospective switchback type of experimental design and that one can inject science into an otherwise largely empirical function, some purpose will have been served by this. I agree there are serious difficulties in attaching what significance there is to the various functions.

KURUVILA (Bombay, India) Does excessive dialysis produce any changes in the parameters you showed?

TESCHAN Sure! That is the next question, you see, as to whether doing more dialysis would be better. All we have looked at so far is reductions based from a preconceived baseline. Those studies are specifically underway now.