EFFECT OF RAPID HAEMODIALYSIS ON CSF PRESSURE AND WATER CONTENT OF CEREBRAL TISSUES IN DOGS*

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INTRODUCTION
Neurological complications occasionally develop following otherwise successful haemodialysis of uraemic patients. It has been suggested that haemodialysis brings about a rapid decrease in the concentration of urea in the circulating blood without a corresponding fall in cerebral tissues and that, because of the difference in urea concentration, water might be expected to enter cerebral tissues and cause them to swell. The experiments to be described are a part of a study designed to elucidate this problem.

METHODS
Mongrel dogs were made uraemic by ligation of both ureters 48-72 hours before the start of dialysis. The urea content of the plasma was further increased by a slow infusion of hypertonic urea solution at least 24 hours before dialysis. The dogs were anaesthetized with Nembutal and haemodialysis was carried out with the Travenol twin-coil artificial kidney, using isotonic bath fluid containing 140 mEq sodium per litre. Duration of dialysis was usually 60 minutes. Serial blood samples were taken for osmolarity, urea, electrolytes and arterial pH, pCO₂ and bicarbonate. Dry weight, urea, sodium and potassium were determined in cerebral cortex tissue and in white matter. Three groups of normal dogs were also subjected to haemodialysis, the first group with isotonic bath fluid, the other two with hypotonic bath solutions containing 90 and 50 mEq sodium per litre, respectively. CSF pressure, without loss of CSF fluid, was measured during some experiments.

RESULTS
We have previously reported the effect of haemodialysis on the urea content of blood and cerebral tissues of uraemic dogs (Dossetor and Pappius, 1964). Urea content of cerebral tissues in uraemic dogs was in equilibrium with that of plasma prior to dialysis. Rapid haemodialysis resulted in a sharp decrease in the concentration of plasma urea, which was accompanied by a considerable, but slower, decrease in the urea content of cerebral tissues. The decrease in the white matter was always less than in the grey. Following dialysis urea levels in the plasma increased significantly and equilibrium was reestablished within the first hour after dialysis.

We may now consider whether cerebral swelling was induced in the brain tissue by these experiments. In experiments in which several biopsies were taken it was found that in control, non-dialysed, normal and uraemic animals, traumatic damage involved in earlier biopsies caused some swelling in the tissue removed in subsequent biopsies, thus masking the effect of dialysis in the dialysed animals. To avoid these complications brain biopsy was taken only at the end of 60 min. dialysis and results compared with values obtained in other, non-dialysed uraemic or normal dogs. These results are seen in Figure 1.

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EFFECT OF HEMODIALYSIS ON DRY WEIGHT OF CEREBRAL TISSUES OF DOGS

White Matter

Gray Matter

- Normal Dogs Before and After Isotonic Dialysis
- Normal Dogs After Hypotonic Dialysis - Bath Sodium 90 m eq/l
- Normal Dogs After Hypotonic Dialysis - Bath Sodium 50 m eq/l
- Uremic Dogs Before and After Isotonic Dialysis
- Average ± SEM
a. Brains of uraemic dogs: isotonic haemodialysis

Changes in dry weight of cerebral tissues can be converted to per cent swelling by a formula published some years ago by Elliott and Jasper (1949). The results in Figure 1 are presented as mg of dry weight per 100 mg of tissue and the scale for per cent swelling is also included. The standard deviation of average pre-dialysis dry weight was equivalent to less than ±5% swelling for both white and grey matter. ±5% swelling was taken as the normal range.

Pre-dialysis dry weight of cerebral tissues was the same in normal and in uraemic animals. Rapid haemodialysis of uraemic dogs resulted in a decrease of average dry weight, i.e. produced swelling, of both white matter and the cerebral cortex. In both tissues the difference from pre-dialysis values was statistically highly significant even though cerebral swelling was not always produced. Dry weight within normal limits was found in cerebral cortex of 8 of the 18 dialysed dogs and in white matter of 6 of the 18.

The dog may not be the best species for this type of study. The dog is the smallest animal which can be dialysed rapidly with the standard artificial kidney. On the other hand, there is experimental evidence that dog brain is more permeable to urea than cat or rabbit brain (Bradbury and Coxon, 1962; Reed and Woodbury, 1962). We are confident, however, that this is only a relative difference which makes the demonstration of a concentration gradient for urea more difficult in the dog, but which does not invalidate our findings.

b. Brains of normal dogs after isotonic haemodialysis

In a control group, 8 normal animals were dialysed with isotonic bath fluid. Dry weight of cerebral cortex was normal. A significant though very slight swelling of white matter was observed, which remains unexplained.

c. Brains of normal dogs after hypotonic haemodialysis

When normal dogs were dialysed with hypotonic bath fluid containing 90 mEq sodium per litre significant decrease in dry weight of white and grey matter was observed, but again cerebral swelling was not an invariable finding. Three normal animals were subjected to haemodialysis with bath fluid containing only 50 mEq sodium per litre. All died approximately 30 minutes after the start of dialysis, at which time there was swelling of cerebral cortex in all three and two of the three showed considerable swelling of the white matter.

In general, however, we have to conclude from these experiments that cerebral tissues are fairly resistant to osmotically induced swelling.

d. CSF pressures

In a number of animals CSF pressure was measured during dialysis. When normal dogs were dialysed with isotonic bath fluid (140 mEq Na per litre) no significant change in CSF was observed. The pressure recorded at the end of 60 min. dialysis was never higher than at the start. In contrast dialysis of normal dogs with hypotonic bath fluid and of uraemic dogs with isotonic bath fluid resulted invariably in an increase in CSF pressure. However, the animals with greatest increase in CSF pressure were not necessarily the ones in which cerebral swelling was demonstrated and the changes in CSF pressure could not be correlated with the presence or absence of swelling, nor were they correlated with the degree of swelling when it was present. It thus appeared that other factors besides cerebral swelling must contribute to the increase in CSF pressure associated with haemodialysis and urea, and sodium analyses were done on CSF in order to compare CSF/plasma concentration gradients with brain/plasma gradients. These comparisons are seen in Table I. In all experiments, urea content of CSF was not greatly affected by dialysis, so that a considerable concentration gradient for urea was established between plasma and CSF, greater in fact than that between plasma and cerebral tissues.
TABLE 1
Pre-dialysis and post-dialysis concentration ratios

<table>
<thead>
<tr>
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<th>CSF/Plasma</th>
<th>White Matter/Plasma</th>
<th>Cortex/Plasma</th>
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<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
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<tr>
<td><strong>Urea</strong></td>
<td></td>
<td></td>
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<tr>
<td>(Isotonic dialysis of uraemic dogs)</td>
<td>0.86</td>
<td>1.83</td>
<td>0.97</td>
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<tr>
<td><strong>Sodium</strong></td>
<td></td>
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<tr>
<td>(Hypotonic dialysis of normal dogs)</td>
<td>152 ±5</td>
<td>142 ±5</td>
<td>—</td>
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<tr>
<td></td>
<td>146 ±4</td>
<td>110 ±4</td>
<td>—</td>
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<tr>
<td></td>
<td>1.04</td>
<td>1.29</td>
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Results in italics = p < 0.01

As with urea in isotonic dialysis of uraemic dogs, so with sodium in hypotonic dialysis of normal dogs; in both a greater concentration gradient developed between plasma and CSF than between plasma and cerebral tissues. This may be considered as a basis for osmotic movement of water into CSF space and may be responsible for the consistent increase in CSF pressure which was observed.

CONCLUSIONS

In conclusion, we have demonstrated that in a majority of uraemic dogs rapid haemodialysis resulted in cerebral swelling. However, an increase in CSF pressure was a more consistent finding. Our results suggest that osmotically induced changes in the volume of CSF under these experimental conditions may be a factor contributing to the increase in CSF pressure.

It is at present not known whether the neurological complications associated occasionally with haemodialysis of uraemic patients are only related to the increase of CSF pressure, so consistently demonstrated in our experiments, or whether they would occur only in those patients or animals in whom brain swelling also occurred. Other gradients, e.g. hydrogen ion concentration gradients, have not been studied adequately in this syndrome.

REFERENCES


DISCUSSION

The CHAIRMAN: Those have been three very fascinating papers on this very important aspect of haemodialysis. I shall now open the discussion on those papers.

Dr. S. T. Boen (Amsterdam): I should like to comment on Dr. Drukker’s paper and give a word of warning about using high dextrose concentration in the bath fluid for prevention of disequilibrium syndrome. The blood sugar level achieved with this procedure depends on the rate of production of insulin by the patient. We have observed one patient who reacted very well during the first two runs but developed a disequilibrium state after the fourth dialysis because his own pancreas apparently reacted by forming more insulin. We did not achieve a high glucose concentration at that point and he developed convulsions.

I should like to ask Dr. Drukker whether he made some studies on repeated dialysis.

Dr. W. Drukker (Amsterdam): May I answer Dr. Boen?

We did some studies on patients who were repeatedly dialysed in this way with high glucose concentrations. I must admit that glucose levels in many cases were different and that they were not predictable. We feel however that high glucose dialysate concentrations, like 2%, are still better than a low one. This has been confirmed by the work of Dr. Bennhold, but I am aware that dialysing patients with very high urea levels in the blood, still offers more risk than dialysing them at lower levels.

When we have to repeat dialysis we start at lower urea levels. The majority of the acute patients admitted to our unit are in bad condition with very high BUNs – sometimes 300 mg%, which is nearly equivalent to 600 mg% urea – and when we do repeated dialysis we mostly start dialysis at 150 mg% of BUN. So, then, the problem is not as big as at the first dialysis. The risk is much less. I still feel that the only thing we can do when we have patients with acute renal failure in bad condition and high BUNs is to put them on a high glucose concentration in the bath.

The CHAIRMAN: Dr. Kennedy, would you like to make your comment?

Dr. A. C. Kennedy (Glasgow): Dr. Drukker has given a very convincing demonstration that a concentration of bath glucose of 2 g is better that 1.5 g in preventing plasma osmolality changes. In our original studies on this we stopped at a concentration of 1.5 g because at that level we seemed to have largely, if not entirely, eliminated the clinical consequences of cerebral disequilibrium, but perhaps we should go up to the 2 g% level.

I should like to comment on Dr. Bennhold’s paper. I think there was a broad correlation shown between bath glucose concentration and E.E.G. changes in that more patients who were dialysed against a low concentration—that is 0.5 g—showed deterioration than when the concentration was higher, although some did deteriorate. I should like to ask her two points.

First, what concentration of glucose she recommends now for use in the bath?

Secondly, what does she think causes the occasional abnormal E.E.G. records before dialysis?

Dr. I. Bennhold (Berlin): We prefer, in any case, the 1.5 g.% glucose concentration for the acute cases, but for the chronic ones we think it does not matter which one we use.

And now the second question: Though we were looking for them, we do not know the causes which really produce these predialysis E.E.G. changes. However, we supposethat they are also due to a certain cerebral oedema.
Dr. J. L. Funck-Brentano (Paris): I should like to comment briefly on the problem of cerebral oedema of these patients. The so-called extra-cellular phase of the brain is very small: about 3% of all the cerebral content of water. So when one increases the extra-cellular hydration of the whole body by giving water plus NaCl it should not have much influence on the cerebral content of water and on development of cerebral oedema. As far as the blood pressure remains normal this extra-cellular overhydration should not bring on any impairment of the E.E.G. True oedema of the brain should result from a global overhydration of the cerebral tissue by giving water alone, creating a real 'water intoxication'.

Two groups of rabbits have received the same quantity of water. In the former group the water was given alone, so it could create a total overhydration. The latter group received water + NaCl in such a rate that osmotic pressure of the blood remains at a normal level and that the water given remains inside the so-called extra-cellular space (Figure 1).

![Graph showing E.E.G. responses](image)

Fig. 1. Influence of overhydration of the E.E.G. of rabbits.
Up: water alone, impairment of the E.E.G.
Down: water plus NaCl, normal E.E.G. (The two groups of rabbits have received the same quantity of water).

Figure I shows you that in group I receiving water alone, a supply of water corresponding to an increase of weight of about 10%, provokes some alteration of the E.E.G. In group II, receiving water plus salt, no modification of the E.E.G. was observed for the same increase of weight.

I should like to compare this fact with what has been said by Dr. Bennhold who observed some alterations of the E.E.G. in patients placed on artificial kidneys with a low concentration of glucose in the bath. This condition favours a total overhydration similar to the one we have observed on rabbits receiving water alone.
DISCUSSION

Dr. H. Tenckhoff (Seattle): Concerning Dr. Kennedy's question as to the aetiology of the E.E.G. changes and convulsions; they are quite frequently observed in a number of clinical conditions associated with acute or chronic renal failure, such as over-hydration which we see very often when patients come to our clinics, or metabolic encephalopathy or hypertensive encephalopathy. We cannot assume that they are always due to urea per se.

To stress Dr. Drukker's point and also Dr. Boen's point on the individual variability of glucose response and E.E.G. changes, I should like to report on an 8-year old girl whom we are dialysing chronically with an on-going B.U.N. below 100 mg. %—on an average about 80 mg. %. This little girl, although we dialysed her with a reduced Kiil dialyser, a half-size Kiil dialyser, regularly developed during the first 2 hours E.E.G. changes, occasionally with convulsions. Those could only be controlled after we increased the glucose concentration by adding up to 2.5–3 g % to the dialysate fluid. At that point she developed severe hypoglycaemic shock with convulsions after the dialysis. Subsequently her dietary protein intake was cut to 1 g/kg bodyweight which reduced the average on-going BUN to about 60 mg % and convulsions have not occurred since.

Dr. S. Shaldon (London): I think Dr. Dossetor's observation that there seems to be a lag in sodium equilibrium across the dog's cerebrospinal meninges is extremely interesting. I think that, to date, nobody has shown that this lag exists in man but it could be that we have not studied the sodium disequilibrium sufficiently in some of our chronic patients, particularly. We have observed an exactly similar phenomenon to Dr. Tenckhoff's where urea clearly could not explain the manifestations of the disequilibrium in terms of the osmotic drop in the plasma. In this particular patient hypernatraemia was present at the start of dialysis, relatively—that is to say a serum sodium of 140 in a patient who had been eating a lot of salt and not drinking any water. We think possibly that the disequilibrium was produced with a bath sodium of 130. I wonder whether we should not pay more attention to the possibility that a disequilibrium of the sodium may be responsible for cerebral symptoms in some of these patients.

Dr. D. N. S. Kerr (Newcastle): I should like to ask Dr. Bennhold whether she has any observations on the duration of her E.E.G. changes. I think I saw on her slides up to 90 minutes. It is about 90 minutes after dialysis when our patients start thinking of driving home and I have no idea what these E.E.G. changes do to their driving skill.

Dr. I. Bennhold (Berlin): Well, our patients do not go home by car but they are quite fit and they walk home 90 minutes after dialysis; Because they go home at this stage we cannot make further investigations and we do not want to keep them in hospital longer.

Dr. H. G. Siebeth (Cologne): We have measured sodium concentrations up to 180 mEq/l. in cerebrospinal fluid and in plasma in the same patient only to 145 mEq/l. There is a great difference between plasma and cerebrospinal fluid.

On the other hand, I should like to ask: have you seen, during the dialysis, a drop of the plasma sugar towards the end of the dialysis? We have often seen that at the end of the dialysis there is the same blood flow and the same sugar concentration in the bath as in the beginning but a drop in plasma concentration.

Dr. W. Drukker (Amsterdam): After dialysis there was a rather marked decrease of blood glucose. Then, as I mentioned, between 1 and 3 hours you have to watch that slight signs of disequilibrium may still occur but not during dialysis. When you have a patient who may be in danger of getting convulsions, as we had, then you have to give him a glucose solution intravenously after dialysis.
DISCUSSION

Dr. G. M. ABER (Birmingham): I wonder if Dr. Dossetor could tell us what the results of his pH and particularly pCO₂ changes were in relationship to his relatively acute studies, and whether these were in any way tied up with the changes in intracerebral C.S.F. pressures?

Dr. J. B. Dossetor (Montreal): We wanted the arterial pCO₂ for the very reason that was mentioned, because of the fact that CO₂ controls brain swelling. We have only reported on the results of those in which the pCO₂ remained within the normal range.

I have no other comment.