THE ELIMINATION OF N.P.N., CREATINE AND URIC ACID IN RELATION TO THE DURATION OF EXTRACORPORAL HAEMODIALYSIS

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Miller et al. (1) and Albers (2), following the work of Wolff et al. (3) on the dialysis of several substances, have established the best method for measurement of haemodialysis.

They calculated the optimal bath-volume, frequency of change of the bath and rate of blood-flow. They proceeded in all investigations and calculations from a static model- they assumed a constant concentration of urea for the total body-fluid.

As Dost (4) and Mertz (5) pointed out in the case of plasma in which there is a falling concentration of a substance then the concentration of this substance in the various body-fluids will not be equal and the system will not come to equilibrium. These authors themselves noted that their calculations did not take account of this factor and also of the synthesis of urea during haemodialysis.

We wanted to find out the rates at which N.P.N., creatinine and uric acid were eliminated and what clinical effects any differences would give rise to.

METHOD

Our investigations were made with the three-coil kidney of Kolff and Watschinger (6) with a surface of 26,400 cm$^2$ and with a 100 l. bath of usual mixture. The extracorporeal-blood-volume was 1000 to 1200 ml. The flow of blood was kept constant during dialysis, the range being 230 to 300 ml./min. The bath was changed regularly every 1 1/2 hours, the break in the dialysis lasted about 5 mins. The concentration of N.P.N. (nitrogen in bath), creatinine (7) and uric acid (8) in plasma and in the bath were measured at the beginning and at every change of the bath water. The blood was taken from the radial artery. The results were obtained from 20 dialyses, these being from 7 patients with acute renal failure and two patients with chronic renal disease, both sexes and between 20 and 68 years old. Cerebro-spinal fluid was obtained and CSF pressure was measured using a permanently inserted needle.

RESULTS

The early rapid, and later asymptotic drop in the plasma concentration to the time axis for N.P.N., creatine and uric acid is well known. Were the concentration in plasma representative for all the body fluid, as is assumed in the calculations of Miller and Albers, then the graph, on half-logarithmic paper, would be expected to be a straight line, as an exponential function. Figure 1 shows, however, that the graph of percentage drop in plasma concentration (average of all dialyses) is a curve convex to the origin. The percentage drop, as measured by the total amount of substances in bath, gives, on the other hand, a straight line.

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We interpreted the curve as showing that urea, creatine and uric acid were diffusing into the extracellular fluid and that it was this that caused the curve to deviate from the linear particularly near to the end of dialysis. Also we calculated from the fall in plasma concentration during each dialysis period the amount of N.P.N., creatinine and uric acid that could come from the extracellular fluid (ECF) (ECF = 20 or 30% bodyweight) and expressed this as a percentage of the total amount found in the bath in the same period. It is clear that we are dealing only with an approximate quantity as between plasma and different parts of the ECF there is not complete equilibrium and because of this the right quantity may be somewhat smaller. Because a proportion of the patients were hyperhydrated, the ECF was taken as 20 or 30% of the bodyweight. Figure 2 shows the results for N.P.N. or nitrogen (average of 20 dialyses), Figure 3 for creatinine (average of 17 dialyses) and Figure 4 for uric acid (average of 14 dialyses). These show that the percentage amount coming from the ECF became smaller as the dialysis progressed. The same is also true for creatinine and uric acid. The proportion of creatinine and uric acid in the ECF is notably greater than that of nitrogen; the nitrogen being formed in the case of uraemic patients 95% from urea. This difference is due to the different rates of diffusion of urea, creatinine and uric acid in the body and on the dialysis membranes.

We calculated the total amounts/kg. body-weight of urea nitrogen, creatine and uric acid in the bath and then put these figures as percentages of the amounts eliminated from 1 l of plasma, estimated from the fall in plasma concentration during complete dialysis. These percentages are shown in Figure 6. For example: amount eliminated/kg. bodyweight 800 mg; drop in concentration in plasma 100 mg.% = 1000 mg./l. of plasma. So amount/kg. bodyweight = 80% of the amount/l. of plasma.

One can assume that the body water is about 60-70% of the bodyweight and that therefore the total amount that has diffused/kg. body-weight should be at the most 60-70% of the amount from 1 l. plasma; assuming equilibrium between all body fluids at the end of dialysis. This is the case with creatinine with 45% and uric acid with 51%. However for nitrogen, and therefore with urea, with 84% the percentage is too large. Seven dialyses from a patient with an acute attack of chronic pyelonephritis were not included in this Figure. This patient had a temperature between 38,5° and 39,5°C. In none of the 7 dialyses was the percentage below 100 and the average was 113%. There was no difference from the previous dialyses in the case of creatinine and uric acid. We explain the increase in the case of nitrogen as coming from new synthesis of urea during dialysis. This explains especially the high value for the patient with strongly increased katabolism during fever. We cannot say whether a restraint would occur on the urea cycle because of the high level of urea, which in dialysis is artificially lowered.

We explain the large quantities of urea, creatinine and uric acid that are eluted into the first bath from the ECF and the drop in the following baths as follows: At the start of dialysis there is a large concentration gradient between the bath and the plasma or the ECF; on the other hand there is equilibrium between ECF and intracellular fluid (ICF). It follows that larger quantities of urea etc. diffuse from the ECF into the bath than from the ICF into the ECF. There is, therefore, an increasing concentration
gradient between ICF and ECF. As this concentration gradient increases so do the amounts diffusing from the ICF into the ECF. As the dialysis progresses the concentration gradient between ECF and bath and also the amount being eluted decrease. After a maximum it is probable that the concentration gradient between ICF and ECF also falls. In a few cases at the end of dialysis we observed that not only did the concentration of urea in plasma not decrease but that it actually increased although urea was still diffusing readily into the bath. It appears therefore, that more urea is diffusing into the ECF from the ICF than is diffusing out into the bath. These differences in urea concentration in the various body fluids lead to osmotic gradients and the subsequent movement of water in the opposite direction to that of the urea (Figure 6). In this figure the plasma and ECF are only divided for the purpose of illustration.

The same arguments as were used with ICF and ECF also apply to the cerebrospinal-fluid and the plasma.

The measurement of the cerebrospinal fluid pressure shows a sharp rise at the beginning of dialysis. At the end of dialysis the pressure dropped once more (Figure 7). This observation is in agreement with that of Gilliland and Hegstrom\(^\text{(10)}\) who observed the cerebrospinal-fluid-pressure of uraemic dogs during dialysis. Sitprija and Holmes\(^\text{(11)}\) found an increase of intraocular pressure during dialysis in man.

The N.P.N. concentration in plasma and cerebrospinal fluid of another patient is shown in Figure 8. Before the dialysis the urea concentration in cerebrospinal fluid, calculated from N.P.N., was somewhat lower than in plasma. During the dialysis the plasma concentration falls far below that of the cerebrospinal fluid. This result was found by Kennedy et al\(^\text{(12)}\) and Scheitlin and Hunzinger\(^\text{(13)}\). Tiredness, head-aches, confusion, vomiting, muscular trembling and convulsions during dialysis can be explained by this increase in cerebrospinal-fluid-pressure. These symptoms are greater when the concentration of urea is high and when the reduction in concentration is rapid. Addition of urea to the bath\(^\text{(10)}\) and infusion of urea\(^\text{(12)}\) cause a reduction in the cerebral symptoms. That an intracellular oedema in the brain causes these symptoms is probable although not yet certain.

We have already pointed out that osmotic pressure will in all likelihood be created in other organs by these differences in urea concentration between ICF and ECF. Although the movement of water into cells due to such osmotic pressure can be assumed, it has not yet been demonstrated.

Whether such movement of water gives rise to clinical symptoms, with exception of cerebral symptoms during dialysis, cannot be said. It is perhaps worth noting that the increase in blood-pressure during dialysis also could be due to movement of water into the muscles of the artery walls.

With other more experienced authors we believe that a slower dialysis would be better for the patients because then there would not be so rapid a drop in the concentration of urea in the ECF and so fewer cerebral complications would occur. For the same reason it is important to begin the dialysis with a low N.P.N. concentration of about 150 mg.% and urea concentration of 300 mg.%. With these precautions not only the central nervous symptoms, but also other severe uraemic symptoms such as uraemic haemorrhage, would be reduced.
REFERENCES

Figure 1. Percentage decrease in concentration in plasma during haemodialysis and also total amounts in 4 dialysates. (Semilogarithmic scale.)

Figure 2. Source of dialysed N.P.N. from extracellular fluid in 4 baths (/// ECF = 20%, --- ECF = 30% of body weight).

Figure 3. Source of dialysed creatinine from extracellular fluid in 4 baths. (/// ECF = 20%, --- ECF = 30% of body weight).

Figure 4. Source of dialysed uric acid from extracellular fluid in 4 baths. (/// ECF = 20%, --- ECF = 30% of body weight.)
Figure 5. Amount of dialysed N.P.N., creatinine and uric acid as a fraction of kg body weight expressed as percentage of the decline in plasma concentration.

Figure 6. Schematic representation of urea concentration during dialysis. Bath(B), Plasma(P), Extracellular Fluid(ECF), Intracellular Fluid(ICF).

Figure 7. Pressure in the cerebrospinal fluid during haemodialysis.

Figure 8. N.P.N. concentration in plasma and cerebrospinal fluid during haemodialysis.
A.C. KENNEDY (Glasgow): As the speaker has indicated, the differential clearance of urea and other substances from the cerebral-spinal fluid during dialysis has been well documented by various people. Regarding the prevention of this, you mention the desirability of going in early with dialysis and preventing the urea rising to precipitous levels and having a very rapid fall. I think we would all agree with this, partly on general grounds in the treatment of uraemia, and partly because of the cerebral dialysis syndrome. However, there are circumstances in all artificial kidney units when one is faced with the position that the patient has a very high urea and this is the starting point with this patient. In this setting I think it is important sometimes to bring the urea down rapidly. We have shown to our satisfaction that this can be done without producing cerebral symptoms by increasing considerably the concentration of glucose in the bath.

O. KORALNIK (Geneva): I should like to ask whether you do not think you make an oversimplification when you speak about the pressure of the cerebro-spinal fluid, because there is not always a parallelism between the increase in the volume of, let us say, the brain and the pressure of the cerebro-spinal fluid; that would be too simple. It is perhaps true in an acute swelling or decrease of volume, but not in a longer run, because you do not know anything about the formation and the resorption of the cerebro-spinal fluid. You can speak of that experimentally, or if you have a flap, or if you measure the intra-ocular pressure, but you cannot just make a tap and see what the pressure is. That does not really tell you anything about the volume of the brain.

H.G. SIEBERTH (Freiburg): We have no method by which to measure the volume of the brain. We can only measure the pressure of the cerebro-spinal fluid.

C.L.J. VINK (Eindhoven): May I ask Dr. Sieberth whether he adds glucose to the dialyzing bath, or other substances, to prevent this pressure?

H.G. SIEBERTH (Freiburg): We have not done these experiments, but they have been made by other authors; there is a publication by Dr. Kennedy. We have ultra-filtrated during dialysis and the cerebral symptoms have then been decreased.

C.L.J. VINK (Eindhoven): Yes, that is so. May I ask your and Dr. Kennedy's opinion about our dehydration technique in these conditions?

If an osmotic equilibrium exists between the blood and the dialysis fluid, ultrafiltration will mainly result in an isotonic dehydration of the extracellular compartment. This generally will, but does not necessarily, imply that cerebral edema decreases; especially not as the concentration difference of the blood-C.S.F. for urea during dialysis may cause a net osmotic water movement into the cerebral compartment. This effect can be opposed by increasing the osmotic pressure of the extracellular ions: sodium and chloride. Therefore our therapy is to give orally during the dehydration some tablets of NaCl if it is tolerated by the cardiovascular system (blood pressure etc.). Solutions of sugars, however, introduce extra water and give a rebound effect.
A.C. KENNEDY (Glasgow): I have not made any observations on this, but I think it would be an attractive thing to do.

Perhaps I may also make a comment on something said by a previous speaker here. I would agree that it is unwise to draw conclusions from the pressure recordings in a spinal manometer as to what is happening in the brain during dialysis, but we have found a very convenient way of studying this by doing continuous electroencephalographic recordings during dialysis. This certainly gives an indication of some disturbance in the brain, although I do not know precisely what it is.

THE CHAIRMAN, F.M. Parsons (Leeds): Is there any difference in the clinical course of two patients with the same degree of uraemia, the one being a chronic case and the other an acute case?

H.G. Sieberth (Freiburg): We have treated only acute renal failure and not chronic. We have treated chronic too, but only with an acute attack of pyelonephritis.

A.C. KENNEDY (Glasgow): We have treated both acute and chronic, and the chronic tolerate a rapid drop in urea less well than the acute.

THE CHAIRMAN: This raises the issue as to whether this is the one and only story associated with the so-called 'disequilibrium syndrome'. That concludes this morning's session.