Prevention of dialysis disequilibrium syndrome by use of high sodium concentration in the dialysate

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Prevention of dialysis disequilibrium syndrome by use of high sodium concentration in the dialysate. Nine patients, including four undergoing their first hemodialysis, were observed clinically and by hourly electroencephalographic recordings before, during, and three hours after highly efficient hemodialyses during which plasma osmolality was maintained by use of a dialysate with increased concentrations of sodium and chloride. As a control group, 8 patients (five undergoing their first hemodialysis) were similarly studied but with a dialysate of standard composition (Na = 133 mEq/liter). The EEG showed definitely increased abnormality in 10 of 13 control dialyses and in 2 of 9 dialyses in the experimental group ($P < 0.01$). Symptoms suggestive of the dialysis disequilibrium syndrome appeared in nine of the control dialyses but in none of the experimental group ($P < 0.001$). No ill effects from increased dialysate sodium concentration could be demonstrated during or after a single hemodialysis.

Prévention du syndrome de déséquilibre de la dialyse au moyen d'une concentration de sodium élevée dans le dialysat. Neuf malades, dont quatre subissaient leur première hémodialyse, ont été observés cliniquement et au moyen d'enregistrements électro-encéphalographiques horaires pendant et trois heures après des hémodialyses très efficaces où l'osmolalité plasmatique était maintenue constante grace à un dialysat dont les concentrations de sodium et de chlore étaient augmentées. Un groupe contrôle de 8 malades, dont cinq subissaient leur première hémodialyse, a été étudié de la même façon alors que le dialysat avait une composition standard (Na = 133 mEq/l). L'électroencéphalo-gramme a montré une augmentation patente des anomalies chez 10 des 13 contrôles et chez deux des neuf sujets du groupe expérimental ($P < 0.01$). Des symptomes suggérant un syndrome de déséquilibre au cours de la dialyse sont apparus chez neuf sujets du groupe contrôle mais seulement chez un sujet du groupe expérimental ($P < 0.001$). Aucun effet nuisible du à l'augmentation de la concentration du sodium n'a pu être mis en évidence pendant ou après une unique hémodialyse.

The dialysis disequilibrium syndrome is a clinical disorder occurring during or immediately after dialysis. Its symptoms and signs range from frequent minor symptoms such as headache, nausea, vomiting, and drowsiness to more severe disorders such as asterixis, involuntary jerking movements, disorientation, psychosis, convulsions, and coma. Paradoxically, these unfavorable clinical disorders develop while the chemical abnormalities in the blood are improving [1, 2]. The disorder is accompanied by deterioration of the electroencephalogram with slowing of basic rhythms and paroxysmal discharges, suggesting that the clinical manifestations are attributable to cerebral dysfunction [2, 3]. The disorder is most likely to occur in severely uremic patients undergoing their first hemodialysis, particularly when highly efficient dialyzers are used and biochemical abnormalities are corrected rapidly [2, 4, 5], or when the patient has a preexisting neurologic disorder [6].

The pathogenesis of this disorder is in dispute, but the most widely accepted explanation is that overhydration of cells in general and of the brain in particular is caused by an osmotic gradient at the cell wall. During dialysis, the osmolality decreases rapidly in the extracellular fluid and decreases more slowly in the intracellular space, creating an osmotic gradient which favors a shift of water into the cells [3, 7–9].

This study was designed to determine whether maintenance of plasma osmolality would prevent the development of serious symptoms of the disequilibrium syndrome during highly efficient hemodialysis. The osmotic agent used to compensate for the decrease in blood urea was sodium chloride.

Methods

Seventeen patients with severe renal failure were selected for study during 22 hemodialyses. Nine of these dialyses were assigned to the experimental and 13 to the control group. Selection was randomized except for an attempt to allow approximately equal predialysis blood urea concentrations in both groups. Four patients in the experimental and five in the control group were studied during their first hemodialysis, which was performed when endogenous

creatinine clearance had diminished to values below 5 ml/min/1.73 m². The remaining patients were already being maintained by chronic hemodialysis. Five patients were studied under both "experimental" and "control" conditions. The ages of all patients ranged from 17 to 61 years with a mean of 37 years for both groups.

Prior to this study, arbitrary criteria were established. Dialysis disequilibrium was considered to be present if three of the minor, two of the moderate, or one of the severe symptoms or signs developed during dialysis (Table 1). Only the appearance of findings which were not present prior to dialysis was accepted.

Table 1. Symptoms and signs used as criteria for dialysis disequilibrium syndrome

Minor
 Headache; vomiting; drowsiness; restlessness; muscle cramps
Moderate
 Asterixis; myoclonus; disorientation; somnolence
Severe
 Psychosis; convulsion; stupor or coma

Electroencephalograms, including response to photic stimulation, were recorded with an eight-channel electroencephalograph (Grass Model 6) at hourly intervals before, during, and three hours after dialysis (for total periods of eight hours). The electroencephalograms were interpreted independently by one of us (D.W.K.) without knowledge of dialysate composition or clinical symptoms. Recordings were classified by composite characteristics as normal or as abnormal, and abnormalities were divided into three grades based on severity according to the Mayo classification system [10]. Classification was based on portions of the tracings obtained after alerting to ensure comparability among recordings and to exclude simulated abnormality from frequency shifts associated with drowsiness, a common circumstance during dialysis.

Biochemical analyses of arterial blood were performed, before and after dialysis, for blood urea, glucose, plasma creatinine, uric acid, calcium, magnesium, phosphorus, chloride, and acid-base balance. Plasma osmolality, sodium, and potassium were measured at half-hour intervals throughout dialysis and three hours after dialysis. Plasma osmolality was measured in duplicate by the freezing point depression method. Serum sodium and potassium were measured by flame photometry in triplicate. Other measurements were performed by routine laboratory methods.

For high efficiency, two Mini-Kiil dialyzers[1] were used in series with blood flows maintained at 250 ml/min by a blood pump and a countercurrent dialysate flow of 1,000 ml/min from a central tank also in serial circuit. The membrane area totaled 1.28 m². The duration of dialysis was

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[1] Life-Med Mini-Kiil Dialyzers, D3, Life Med Corp., Campton, Calif., U.S.A.
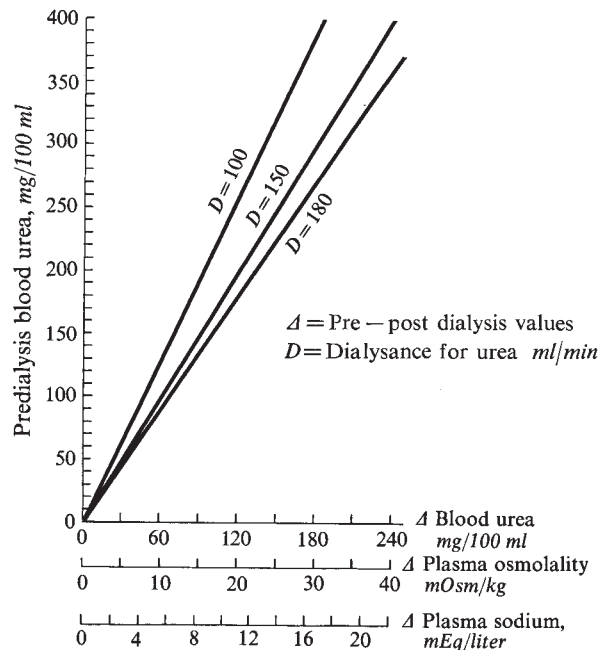

Fig. 1. *Curves used to calculate increase in plasma sodium concentration necessary to compensate for osmotic effect of decrease in blood urea concentration during a 4-hr dialysis, shown for three different dialysance values (D).*
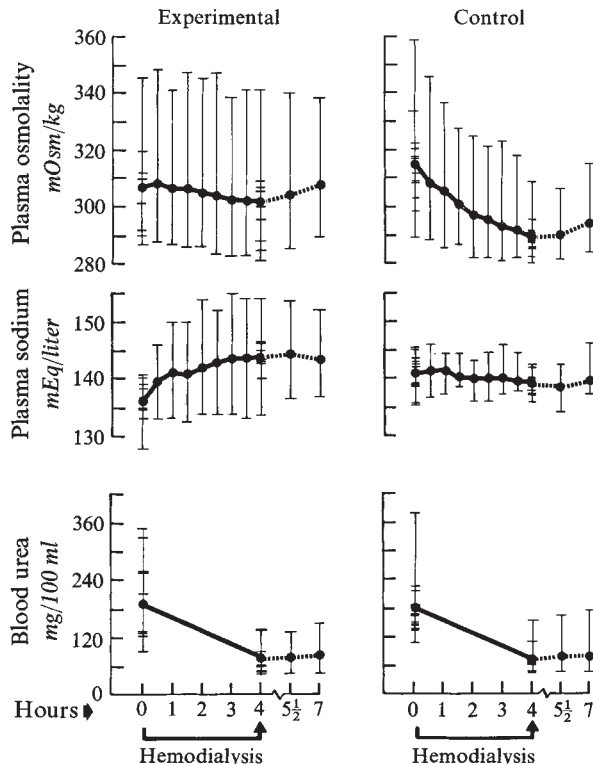

Fig. 2. *Range of blood values during and immediately after dialysis.* Individual cases are shown by horizontal lines at 0 and 4 hr. Scales of ordinates are adjusted so that vertical distance is equivalent to same osmotic effect on all plots. Note that blood urea rather than urea nitrogen values are used.

four hours. The dialysance for urea averaged 165 ml/min with a mean decrease in blood urea concentration of 59%. The negative pressure in the dialysate compartment ranged from 20 to 40 mm Hg. For the control group, a standard dialysate was used containing (per liter): sodium, 133 mEq; potassium, 1 mEq; calcium, 3 mEq; magnesium, 1 mEq; chloride, 108 mEq; acetate, 33 mEq; and glucose, 2 g. The experimental group was dialyzed against a bath of standard composition but with increased concentrations of sodium and chloride achieved by constant infusion of hypertonic saline (3 to 5 g/100 ml) into the dialysate line. Since this infusion contributed less than 3% to the volume of the dialysate, it did not significantly alter the concentrations of the other solutes in the dialysate, but it increased sodium and chloride concentrations in the dialysate to a constant level throughout dialysis. The rate of infusion was adjusted individually in order to achieve an increase in plasma sodium concentration during dialysis sufficient to compensate for the osmotic effect of a decreasing urea concentration and thus prevent a significant change in plasma osmolality. The calculated values for this "Δ plasma sodium" concentration are shown in Fig. 1; however, a dialysate sodium concentration 2 mEq/liter higher than the sum of "Δ plasma sodium" and predialysis plasma sodium concentration was selected to allow for the fact that equilibration of dialysate and plasma sodium is incomplete during a 4-hour dialysis.

Results

Changes in plasma osmolality, plasma sodium, and blood urea for all patients during the four hours of dialysis and the three hours after dialysis are shown in Fig. 2. In the experimental group, plasma osmolality was successfully maintained within a narrow range. The control group showed a marked decrease in plasma osmolality and a slight decrease in plasma sodium concentration. The decrease in blood urea was similar for both groups.

Blood chemical data and changes are shown in Table 2. Dialysate sodium concentrations and changes in plasma osmolality and sodium concentrations showed highly significant differences; the other factors were similar for both groups.

New symptoms or signs observed during or within three hours after dialysis are listed in Table 3. None of the nine patients dialyzed against the higher sodium dialysate fulfilled our predetermined clinical criteria for the dialysis disequilibrium syndrome, despite rapid hemodialysis; nine of the 13 patients dialyzed against standard dialysate fulfilled these criteria (for this difference, $P < 0.001$). Of patients studied during their first dialysis, there were four of five in the control group and none in the experimental group who fulfilled our criteria for this syndrome.

In confirmation of the clinical findings, the electroencephalogram (EEG) showed deterioration in only two

Table 2. Effect of dialysis: Comparison of study groups (Means ± SD)

Observation	Predialysis data			Changes during dialysis[a]		
	Experimental group (N=9)	Control group (N=13)	P	Experimental group (N=9)	Control group (N=13)	P
Dialysate sodium *mEq/liter*	149.3 ± 6.0	133.1 ± 2.6	<0.001	Constant	Constant	...
Plasma osmolality *mOsm/kg*	307.1 ± 18.9	315.0 ± 17.1	>0.05	−5.8 ± 2.7	−25.6 ± 12.9	<0.001
Plasma sodium *mEq/liter*	136.3 ± 4.1	140.8 ± 3.2	≈0.01	+7.5 ± 5.4	−2.2 ± 2.6	<0.001
Blood urea *mg/100 ml*	190.2 ± 101.6	179.0 ± 68.4	>0.05	−114.5 ± 13.3	−106.3 ± 15.3	>0.05
Plasma creatinine *mg/100 ml*	13.4 ± 4.4	14.0 ± 3.2	>0.05	−7.0 ± 3.1	−7.9 ± 2.2	>0.05
Blood glucose *mg/100 ml*	121.8 ± 19.6	117.6 ± 20.9	>0.05	−15.8 ± 19.2	−11.4 ± 28.5	>0.05
Plasma potassium *mEq/liter*	4.9 ± 1.0	5.1 ± 0.8	>0.05	−1.8 ± 0.7	−2.1 ± 0.8	>0.05
Plasma calcium *mg/100 ml*	8.3 ± 1.6	9.1 ± 0.8	>0.05	+1.4 ± 1.1	+1.9 ± 0.8	>0.05
Plasma magnesium *mg/100 ml*	2.44 ± 0.67	2.64 ± 0.51	>0.05	−0.46 ± 0.30	−0.55 ± 0.28	>0.05
Plasma phosphorus *mg/100 ml*	6.1 ± 3.3	5.8 ± 3.5	>0.05	−2.1 ± 2.2	−2.0 ± 1.7	>0.05
Blood pH	7.35 ± 0.04	7.37 ± 0.06	>0.05	+0.08 ± 0.03	+0.11 ± 0.04	>0.025
Blood P_{CO_2} *mm Hg*	43.1 ± 7.7	39.8 ± 5.4	>0.05	−8.9 ± 7.0	−9.1 ± 3.8	>0.05
Blood hematocrit %	21.9 ± 4.2	21.8 ± 4.7	>0.05	−0.9 ± 4.1	+0.1 ± 1.7	>0.05

[a] − designates decrease; + designates increase.

Table 3. New symptoms or signs observed during or after dialysis

Sign or Symptom	Experimental group (N=9)	Control group (N=13)
Headache	1	9
Vomiting	2	5
Drowsiness	3	2
Restlessness	0	5
Asterixis	2	5
Myoclonus	0	1
Psychosis	0	1
Met criteria for syndrome	0	9

of the nine patients in the experimental group, while ten of 13 patients in the control group showed EEG deterioration (Figs. 3 and 4) of one grade or more (for this difference, $P < 0.01$). The two patients with EEG deterioration in the experimental group were studied during their first hemodialysis while four of the five patients of the control group had EEG deterioration during their initial dialysis.

The plasma sodium concentration in the experimental group reached an average of 144 mEq/liter during dialysis (mean increase, 7.5 mEq/liter) and a maximum of 154 mEq/liter in one patient. This increase was not accom-panied by pulmonary congestion, aggravation of hypertension, or weight gain. Pulmonary congestion could not be found at the end of dialysis or three hours later. Diastolic blood pressures decreased by a mean of 8 mm Hg in both groups while systolic pressures increased by 11 mm Hg in the experimental group and by 2 mm Hg in the control group. Body weights diminished during dialysis by means of 0.58 and 0.67 kg, respectively.

At the start of the subsequent dialysis, an average of two days later, body weight and blood pressure (supine position) were compared with those at the end of the previous dialysis. Body weight increased in the experimental group by an average of almost 0.5 kg per day, which corresponds well to the expected increase between dialyses in our experience with "standard" dialysate. In the control group, the mean change in weight was less than 0.05 kg per day. Systolic blood pressures decreased by an average of 8 and 15 mm Hg while diastolic readings increased by 7 and 4 mm Hg, respectively, in the experimental and control groups.

Discussion

The exact pathogenetic mechanism for the dialysis disequilibrium syndrome is not clearly understood [4]. Although this experiment was not designed to study the pathogenesis of the disorder but to test a method for its prevention, the results are consistent with the hypothesis that an
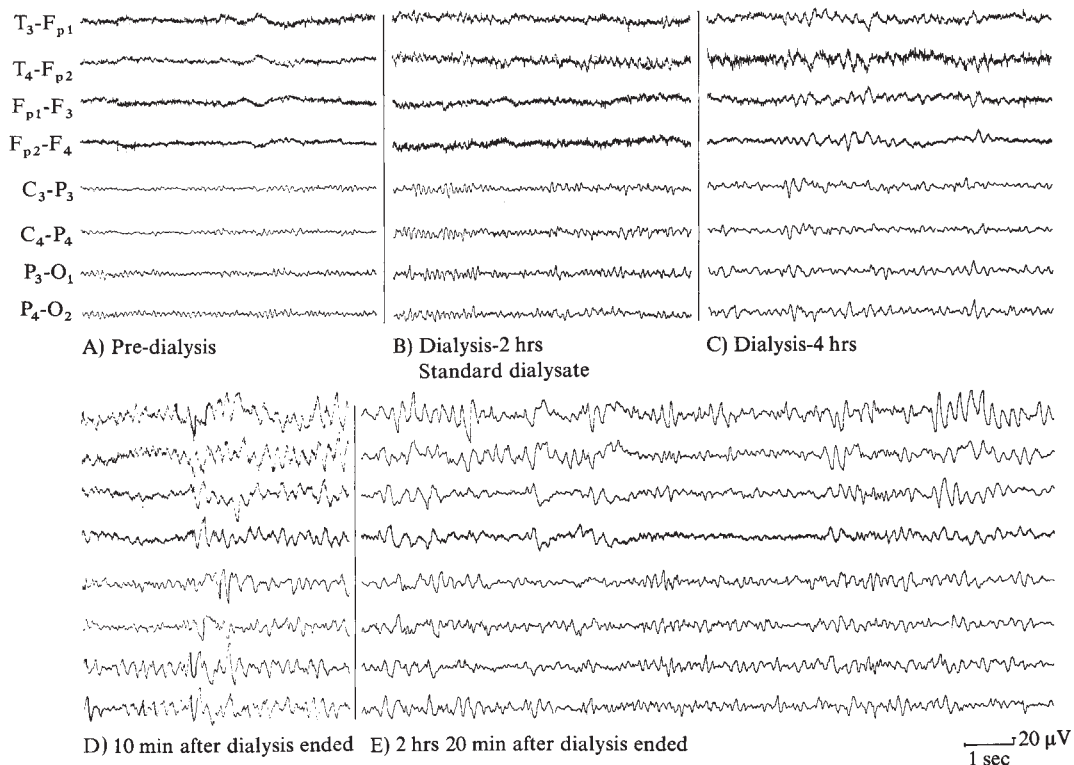

T_3-F_{p1} T_4-F_{p2} F_{p1}-F_3 F_{p2}-F_4 C_3-P_3 C_4-P_4 P_3-O_1 P_4-O_2

A) Pre-dialysis   B) Dialysis-2 hrs   C) Dialysis-4 hrs

Standard dialysate

D) 10 min after dialysis ended   E) 2 hrs 20 min after dialysis ended

20 μV / 1 sec

Fig. 3. *EEG tracings from 41 year-old woman in control group (standard dialysate) who developed the disequilibrium syndrome.* Note normal recording before dialysis *(Upper Left)* and increasing abnormalities consisting of slower frequencies during dialysis (grade 1 in *Upper Middle*, grade 2 in *Upper Right*) and after dialysis (grade 3 in *Lower*).
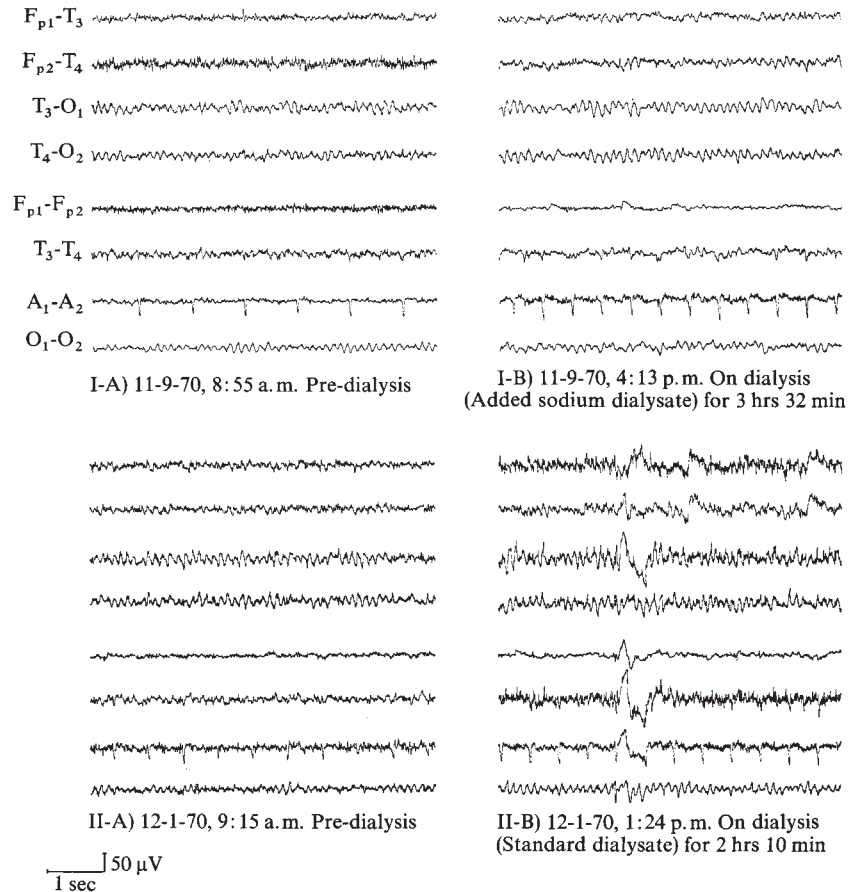
F_{p1}-T_3

F_{p2}-T_4

T_3-O_1

T_4-O_2

F_{p1}-F_{p2}

T_3-T_4

A_1-A_2

O_1-O_2

I-A) 11-9-70, 8:55 a.m. Pre-dialysis

I-B) 11-9-70, 4:13 p.m. On dialysis
(Added sodium dialysate) for 3 hrs 32 min

Fig. 4. *EEG tracings from 51 year-old man (A) before and (B) during dialysis. I,* in experimental group (dialysate with added saline); *II,* in control group (standard dialysate). *Upper,* No change from normal during first dialysis. *Lower,* Change from normal to abnormal (grade 3, paroxysmal) during later dialysis.

II-A) 12-1-70, 9:15 a.m. Pre-dialysis

II-B) 12-1-70, 1:24 p.m. On dialysis
(Standard dialysate) for 2 hrs 10 min

⌐____⌐ 50 µV
1 sec

osmotic gradient at the cell wall, induced by dialysis, may be a major etiologic factor. Alternative explanations include a direct effect of sodium, changes in extracellular fluid volume, ionic gradients at the cell wall, and peripheral effects. Direct measurements of water movement and composition of the brain would be required for proof of such hypotheses.

Kennedy et al [11] and Scheitlin and Hunziker [8] were among the first to call attention to the dialysis disequilibrium syndrome, attributing it to a rapid decrease in blood urea concentration. Alwall [12] attributed the findings of Kennedy's group to water intoxication related to the use of the "rotating drum kidney" which was highly efficient in its removal of urea but incapable of ultrafiltration. Maher and Schreiner [13] also suggested that the disorder is more commonly encountered with the rotating drum dialyzer than with the twin-coil artificial kidney. This may be related to other factors such as greater severity of azotemia in the early days of hemodialysis. The use of less efficient dialysis with shorter periods of dialysis as a means of preventing the disorder has been advocated [1, 2, 6].

Another approach to prevention of the dialysis disequilibrium syndrome has been the addition, to the dialysate, of an osmotic agent capable of blocking the movement of urea into the bath [6, 7, 14] or of diffusing into the bloodstream and thereby also preventing a decrease in serum

osmolality [15]. Osmotic agents commonly used to counteract urea include glucose [7, 16, 17], fructose [7], and mannitol [18, 19].

Several objections may be raised to the use of urea. One of the purposes of dialysis is to remove protein catabolites, including urea. While urea is not highly toxic, it appears to contribute to some of the minor symptoms of the uremic syndrome, such as headache, nausea, and vomiting, and to play a role in the bleeding tendency [20]. In addition, it seems doubtful that a decrease in the blood urea concentration is solely responsible for the dialysis disequilibrium syndrome. In experimental animals, urea loading followed by rapid dialysis produces the anticipated osmotic gradient between cerebrospinal fluid and blood with a significant increase in spinal fluid pressure but without EEG changes [21, 22].

Recent studies by Arieff et al [23] using uremic dogs indicated that during slow dialysis there were no significant osmotic gradients between plasma, brain, and spinal fluid and no increase in brain water or cerebrospinal fluid pressure but, in rapidly dialyzed animals, significant osmotic gradients were established between plasma, cerebrospinal fluid, and brain with increases in cerebrospinal fluid pressure and brain water content. However, they were unable to explain these changes on the basis of changes in concentration of sodium, potassium, or urea; they attributed over-

hydration of the brain to generation of unidentified osmotically active substances within the brain during dialysis. Uremic patients maintained by regular hemodialysis against a high concentration of urea in the dialysate showed only mild symptoms of the dialysis disequilibrium syndrome and no EEG deterioration after rapid decrease of blood urea [20]. Thus, although changes in urea concentration play a major role, they are not the sole cause for the clinical, physiologic, or EEG abnormalities observed during rapid dialysis [9, 14, 20, 21, 24].

Glucose has been widely used as an osmotic agent in dialysates [16, 17]. There are dangers in the use of high concentrations of glucose, such as severe hyperglycemia and hyperosmolality [25] in patients incapable of metabolizing glucose rapidly, or the rapid decrease in glucose concentration and in osmolality after discontinuation of dialysis which may induce a delayed disequilibrium syndrome with seizures [17, 26] or hypoglycemia [27]. Fatalities have occurred during dialyses in which high concentrations of glucose were used [28, 29]. In any case, carefully controlled studies by Hampers et al [24] and Gutman et al [26] failed to show any consistent beneficial effects from a high glucose concentration in the dialysate.

Fructose and mannitol have been proposed because of their slow metabolism [7, 19]. In their extensive studies using mannitol infusions during dialysis, Hagstam et al [19] found that the only consistent beneficial effect was the prevention of muscle cramps.

To our knowledge, sodium chloride has not been proposed as an osmotic agent for prevention of the dialysis disequilibrium syndrome, yet it is known [30] that sodium diffuses more slowly across the blood-brain barrier than urea and that its physiologic effect is of greater duration. A relatively small change in sodium concentration (for example, 1 mEq/liter) can offset the osmotic effect of a seemingly large change in blood urea concentration (12 mg /100 ml). During dialysis, sodium and chloride ions can be removed by ultrafiltration, thereby decreasing the tendency toward increase in total body sodium which might precipitate complications such as acute pulmonary edema and hypertensive crisis. Our interest in sodium as an osmotic agent was stimulated by the articles by Gonzalez et al [31] and Sokol et al [32] in which severe forms of the dialysis disequilibrium syndrome were described in hypertensive patients after the use of a low sodium concentration in the dialysate. Pappius et al [9] and Wakim et al [21, 22] were able to produce EEG changes in dogs simulating those of the dialysis disequilibrium syndrome by dialyzing them against low sodium concentrations in the dialysate. Shaldon [5] found a high incidence of dialysis disequilibrium syndrome in patients with high predialysis serum sodium concentrations, which may suggest that the greater decrease in serum sodium during dialysis is a contributing factor. Edel et al [33] found a low incidence of this syndrome and a small osmotic gradient from plasma to cerebrospinal fluid. However, their center used a dialysate sodium concentration of 148 mEq/liter which is higher than that used in most centers.

Accidental use of a high sodium concentration in the dialysate was reported by Lackenschweiger and Zimmerman [34]. In their center, five patients were dialyzed inadvertently against a sodium concentration of 154 mEq/liter repeatedly for one month but showed surprisingly few side effects.

Our findings of the absence of excessive weight gain, pulmonary congestion, or aggravation of hypertension also demonstrate the infrequency of complications from moderate increases in plasma sodium concentration in a single dialysis. This may be explained by the fact that plasma sodium may increase during dialysis without the diluting effect of water from the intracellular space when plasma osmolality is not significantly increased. The use of higher ultrafiltration also could decrease the problem of volume overload. In repeated dialysis, the use of high sodium dialysate has not been completely evaluated and may be hazardous.

Although this study did not measure the composition of cerebrospinal fluid or brain or the movements of water, the clinical results suggest that major manifestations of the dialysis disequilibrium syndrome can be prevented by maintenance of plasma osmolality through an appropriate increase in dialysate sodium concentration. The level of dialysate sodium may be adjusted individually, thus allowing only a minimal variation in plasma osmolality. Such an adjustment in dialysate sodium concentration seems useful with the first hemodialysis, particularly in patients who are highly susceptible, such as those with greatly increased blood urea concentrations or with cerebral disorders.

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