Experimental dialysis disequilibrium syndrome: Prevention with glycerol

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Experimental dialysis disequilibrium syndrome: Prevention with glycerol. Patients with renal failure being treated with hemodialysis may develop a clinical syndrome characterized by headache, restlessness, nausea, and emesis, which may progress to seizures and coma. An experimental model of this syndrome, called dialysis disequilibrium syndrome (DDS), can be induced by rapid hemodialysis of uremic dogs (BUN, 200 mg/dl; creatinine, 11 mg/dl). In the experimental model, dogs treated with rapid dialysis developed a brain-to-plasma osmotic gradient which resulted in cerebral edema. There was also a fall in both pH of cerebrospinal fluid (CSF) and intracellular pH (pH1) of cerebral cortex and an abnormal electroencephalogram (EEG). The cerebral edema was characterized by an increased osmole content in cerebral cortex tissue. The increased osmole content was not related to retention in brain of sodium, potassium, chloride, urea, or lactate, but was due to undetermined solute (idiogenic osmoles). When dialysis was modified by the addition of mannitol to the dialysate (plasma mannitol, 26 mm), brain edema did not occur, and the fall in brain pH, was prevented. The EEG, however, remained abnormal, and the pH of CSF fell. When dialysis was modified by adding glycerol to the dialysate (plasma glycerol, 26 mm), brain edema did not occur, brain pH, and the pH of CSF were normal, and the EEG improved towards normal. After dialysis with either mannitol or glycerol in the dialysate, idiogenic osmoles were not present in the brain. Eliminating the fall in brain pH appeared to prevent the formation of idiogenic osmoles by cerebral cortex. Thus, DDS was partially prevented by mannitol added to the dialysate. Glycerol, however, not only prevented all the manifestation of DDS but also restored the EEG to a normal pattern. Glycerol may be a useful agent for prevention of dialysis disequilibrium in man.

Prévention par le glycerol du syndrome de déséquilibre de la dialyse. Les malades atteints d'insuffisance rénale traités par hémodialyse peuvent développer un syndrome clinique caractérisé par une céphalée, une agitation, des nausées et des vomissements, et qui peut évoluer vers des crises convulsives et un coma. Ce syndrome a été appelé syndrome de déséquilibre de la dialyse (DDS) et un modèle expérimental peut être réalisé par l'hémodialyse rapide de chiens urémiques (azote uréique, 200 mg/dl; créatinine, 11 mg/dl). Dans ce modèle expérimental les chiens traités par une dialyse rapide développent un gradient de pression osmotique entre le cerveau et le plasma, qui a pour conséquence un œdème cérébral. En même temps, les pH du liquide céphalorachidien et du cortex cérébral diminuent et des anomalies électroencéphalographiques apparaissent. L'œdème cérébral est caractérisé par une augmentation du contenu osmolaire du cortex cérébral. L'augmentation du contenu osmolaire n'est pas liée à la rétention de Na⁺, K⁺, Cl⁻, d'urée ou de lactate mais est due à des substances dissoutes indéterminées. L'addition de mannitol au liquide de dialyse (concentration plasmique de mannitol, 26 mm) empêche l'apparition de l'œdème cérébral et la chute du pH intracellulaire cérébral. Cependant l'EEG reste perturbé et le pH du liquide céphalorachidien diminue. L'addition de glycerol au dialysat (glycerol plasmique, 26 mm) évite l'apparition de l'œdème cérébral et des modifications des pH et détermine une amélioration de l'EEG. Après les dialyse avec du mannitol ou du glycerol les substances dissoutes indéterminées ne sont plus trouvées dans le cerveau. Le fait d'empêcher la chute du pH cérébral semble éviter la formation de telles substances. Ainsi le syndrome de déséquilibre est prévenu par l'addition de mannitol au dialysat. Le glycerol, cependant, non seulement empêche les manifestations de ce syndrome mais ramène l'EEG à une configuration normale. Le glycerol peut être un agent utile pour la prévention du syndrome de déséquilibre chez l'homme.

A complication of treatment with hemodialysis is dialysis disequilibrium syndrome (DDS) [1, 2], which may be characterized only by mild neurological manifestations (headache, restlessness, nausea, emesis), but can progress to seizures and coma. Characteristic alterations in the electroencephalogram (EEG) are also reported [3, 4]. The syndrome is most commonly observed either in patients with acute renal failure who are being treated with their first few hemodialyses or in children [4, 5]. Symptoms of DDS, however, may occur in any azotemic patient, presumably as a consequence of overly rapid correction of biochemical abnormalities. We have previously described an experimental model of DDS in the acutely uremic dog treated with rapid hemodialysis [6]. The syndrome in dogs is characterized by grand mal seizures in the unanesthetized state [6]. Biochemically, there is cerebral edema which is primarily intracellular. The cerebral edema appears to be due to an osmotic gradient induced
from brain to plasma, which leads to a net movement of water into the brain [6, 7]. The osmotic gradient is not related to retention or accumulation in brain of any commonly measured solutes—sodium, potassium, chloride, calcium, magnesium, urea, or lactate [6, 8]. The cerebral edema is accompanied by a fall in both the pH of cerebrospinal fluid (CSF) and the intracellular pH (pHi) of brain tissue (cerebral cortex) [8].

Glycerol, a low molecular weight alcohol (92 mg/mmol), has been used to treat brain edema associated with many different causes, such as acute cerebral infarction and cerebral neoplasm [9–11]. We have shown that in animals, glycerol can be an effective cerebral dehydrating agent in both normal brain and brain with experimental cerebral edema (cold lesion) [12, 13]. Most of the glycerol is metabolized to glucose, water, and carbon dioxide [14–16]. Since its half-life is less than 3 1/2 hr [12], glycerol's accumulation in the body should cause few untoward effects, as may occur with mannitol or other nonmetabolizable solutes. Based on favorable reports of the clinical efficacy of glycerol in several clinical conditions felt to be associated with increased intracranial pressure [10, 15–17], it was decided to evaluate this agent in treatment of DDS. To separate the effects of glycerol from those of hyperosmolality itself, effects of mannitol on DDS were also evaluated.

Methods

Studies were carried out on six groups (total number of animals, 45) of mongrel dogs of both sexes (weight, 16 to 23 kg). The groups were as follows: eight normal dogs (group 1), nine dogs with acute renal failure for 3.5 days (group 2), six dogs with acute renal failure treated with rapid hemodialysis (group 3), eight dogs with acute renal failure treated with rapid hemodialysis where the dialysate was modified by the addition of 35 to 85 mm mannitol (group 4), eight dogs with acute renal failure where the dialysate was modified by the addition of 50 to 100 mm glycerol (group 5), and six dogs treated identically to group 5, but after hemodialysis had been completed (110 min), these animals were observed for an additional 4 hr and then sacrificed (group 6). Acute renal failure was induced in groups 2 through 6 by bilateral ureteral ligation [6].

Electroencephalograms (EEG) were done in all animals. In the animals treated with hemodialysis (groups 3 through 6), EEG's were done prior to dialysis and at 30-min intervals until the conclusion of the experiment. The EEG's were standard eight-channel recordings and were obtained with an electroencephalograph (Beckman Accutrace, Beckman Instruments, Inc., Mountain View, Calif.) with eight subcutaneous needle electrodes [18]. The tracings were analyzed for frequency distribution and power spectrum, as previously described [18].

The intracellular pH (pHi) and extracellular space (ECS) were determined in brain tissue (cerebral cortex) and subcortical white matter of all animals. The ECS was evaluated by determining the distribution of radioactive sulfate in cerebral cortex tissue relative to cortical cerebrospinal fluid (CSF). The pHi of cerebral cortex tissue was determined by the distribution of 14C-dimethadione (DMO) in brain relative to cortical CSF, with the extracellular pH measured in cisternal CSF. The complete analytical methods have been described from this laboratory [19]. In all animals, the pH, P02, Pco2, and bicarbonate concentration were measured in arterial blood and cisternal CSF [6]. In animals treated with hemodialysis, arterial blood gases were measured every 30 min. CSF gases were obtained only twice, at the start and finish of each experiment.

In both cerebral cortex and subcortical white matter of the brain, measurements were made of water content and the concentrations of sodium, potassium, calcium, magnesium, and chloride. Water content was determined by over-drying at 105°C to constant weight. The tissues were then extracted for 24 hr in 750 mm nitric acid; and sodium, potassium, chloride, calcium, and magnesium concentrations were determined in the supernatant. Complete analytical methods have been described [6, 20]. The brain osmolality was measured in a sample of frontal hemisphere that had been rapidly (less than 8 sec) frozen in liquid nitrogen [21]. Glycerol or mannitol were measured in both cortical gray matter and subcortical white matter, as well as in plasma and CSF, of groups 4 through 6. The samples were extracted in 0.5 N perchloric acid and 2.0 N potassium hydroxide [12], and glycerol or mannitol were determined in the supernatants [12, 22].

Additionally, in both plasma and CSF, measurements were made of osmolality and the concentrations of urea, creatinine, sodium, potassium, chloride, calcium, and magnesium [6, 20].

Rapid hemodialysis was carried out with a hemodialysis machine (Travenol RSP) and pediatric coil (0.6m2) at a blood flow of 12 ml/kg and a dialysate
flow of 500 ml/min for a duration of 110 min [6]. Such a dialysis protocol results in a mean fall of plasma creatinine and urea nitrogen by 7 mg/dl (0.62 mmole/liter) and 123 mg/dl (44 mmoles/liter), respectively [6]. These procedures resulted in urea and creatinine clearances of 66.5 ml/min and 63.1 ml/min, respectively (assuming that both urea and creatinine are distributed throughout total body water). In group 3, standard dialysate (Diasol®, Trav- enol Laboratories, Deerfield, Ill.) was used. In groups 4 through 6, glycerol or mannitol was added to the dialysate in quantities such that for the duration of hemodialysis, osmolality of the animal did not change. Based on preliminary experiments in group 5 and 6 animals, glycerol was added to the dialysate such that dialysate osmolality exceeded that of plasma by 15 mOsm/kg of water. With this amount of glycerol, plasma osmolality did not change during dialysis. For group 4 dogs, mannitol was added to the dialysate such that the osmolalities of plasma and dialysate were the same. The net result of dialysis with these modified dialysates was the infusion of either glycerol (groups 5 and 6) or mannitol (group 4) as urea was removed by hemodialysis.

Prior to hemodialysis, animals were sedated with a single i.m. dose of xylazine, 2 mg/kg of body wt (Rompun®, Cutter Labs, Shawnee, Kansas), and then paralyzed with 1 mg/kg/hr of i.v. succinylcho- line (Anectine®, Burroughs Welcome & Co., Research Triangle Park, N.C.). The animals were immediately intubated and mechanically ventilated [6, 19]. The arterial Pco2 was adjusted to about 35 mm Hg, and ventilation was then maintained constant throughout the experiment. EEG's were done before, during, and after hemodialysis, as previously described [18]. Prior to killing all animals, we anesthetized them with sodium pentobarbital (12 to 16 mg/kg i.v.). EEG's were not done after adminis- tration of barbiturate [18].

All values are given as the mean ± SEM. Statistical differences were calculated by Student's t test of group means.

**Results**

*Effects of hemodialysis on blood and CSF.* In nine animals with acute renal failure for 3.5 days, the plasma urea nitrogen and creatinine (± SEM) were 71 ± 6 mmole/liter (199 ± 17 mg/dl) and 1.02 ± 0.03 mmole/liter (11.5 ± 0.3 mg/dl), respectively. (For plasma urea nitrogen, 1 mmole/liter = 2.8 mg/dl, and for serum creatinine, 1 mmole/liter = 11.3 mg/dl.) The plasma osmolality was 341 ± 4 mOsm/kg of water, and osmolality in CSF was 342 ± 4 mOsm/kg of water. Glycerol was less than 1 mmole/liter in both CSF and plasma.

After rapid hemodialysis, the plasma osmolality was 300 ± 2 mOsm/kg, and that in CSF was 318 ± 2 mOsm/kg. The decline in plasma osmolality was primarily due to a fall in plasma urea concentration to 30 ± 4 mmole/liter, and creatinine fell to 5.3 ± 0.7 mg/dl.

After rapid hemodialysis with glycerol in the dialysate (group 5), plasma osmolality was unchanged at 339 ± 3 mOsm/kg. Plasma urea concentration fell by 41 mmole/liter, and plasma sodium concentration, which was 130 ± 4 mmoles/liter in uremic dogs, was 136 ± 3 mmoles/liter after rapid dialysis with glycerol. The CSF osmolality was unchanged at 340 ± 2 mOsm/kg of water, sodium concentration in CSF was 145 ± 2 mmole/liter (predialysis value, 140 ± 4), and CSF urea concentration was 49.4 ± 4.0 mmole/liter (predialysis value, 63.1 ± 4.1). Thus, the net effect of hemodialysis with glycerol was a loss of urea with replacement by both glycerol and sodium, with 65% of the urea lost from plasma being replaced by glycerol. Four hours after completion of dialysis, plasma osmolality (group 6) was 330 ± 7 mOsm/kg, and sodium concentration was 142 ± 4 mmoles/liter.

After rapid dialysis with mannitol in the dialysate (group 4), plasma osmolality was 342 ± 4 mOsm/kg, vs. a predialysis value of 341 ± 6. The plasma sodium concentration was 133 ± 2 mmoles/liter, and plasma urea concentration was 44.9 ± 3.7 mmole/liter (predialysis value, 91.1 ± 5.6). In CSF, osmolality was 337 ± 4 mOsm/liter, vs. a predialysis value of 345 ± 6, and sodium concentration was 140 ± 4 mmoles/liter.

**Mannitol and glycerol concentrations.** When mannitol was added to dialysate (group 4), mannitol concentrations in plasma and CSF were 25.6 ± 2.6 and 4.4 ± 2.0 mmole/liter, respectively. In brain tissue, mannitol was 5.4 ± 0.8 mmole/kg of water in gray matter and 3.9 ± 0.4 mmole/kg of water in white matter.

After hemodialysis with glycerol (group 5), plasma glycerol was 26.4 ± 3.6 mmole/liter, and that in CSF was 4.1 ± 1 mmole/liter. Glycerol in cerebral cortex was 10.0 ± 0.9 mmole/kg of water, and that in white matter was 5.2 ± 1.2 mmole/kg of water.

**Acid-base balance in blood and CSF.** In nine dogs with acute renal failure, arterial pH was 7.22 ± 0.02, Pco2 was 35 ± 3 mm Hg, bicarbonate concentration was 14.2 ± 0.7 mmole/liter, and Po2 was 78
± 4 mm Hg. In CSF, corresponding values were: pH, 7.31 ± 0.02; Pco2, 41 ± 1 mm Hg; bicarbonate concentration, 21.4 ± 1.1 mmoles/liter; and Po2, 58 ± 3 mm Hg.

After rapid hemodialysis, the arterial Pco2 and Po2 were unchanged, the pH rose to 7.32 ± 0.01, and bicarbonate concentration rose to 17.7 ± 0.9 mmoles/liter. In CSF, however, there was a fall in both pH and bicarbonate, despite the rise of these values in arterial blood. The pH in CSF was 7.21 ± 0.02, and bicarbonate concentration was 15.4 ± 0.5 mmoles/liter (P < 0.01).

When mannitol was added to the dialysate (group 4), the arterial blood gases were again not different from values observed after hemodialysis with standard dialysate. Arterial pH was 7.32 ± 0.03, and bicarbonate was 18.9 ± 1.5 mmoles/liter. The decline in pH of CSF, however, was only partially prevented by addition of mannitol to the dialysate. After dialysis with mannitol, pH of CSF was 7.31 ± 0.02 (pre-dialysis value, 7.36 ± 0.02, P < 0.01), and bicarbonate concentration in CSF was 18.1 ± 0.6 mmoles/liter (predialysis value, 21.4 ± 3.5, P < 0.05). Thus, although glycerol in dialysates prevented the fall in pH of CSF, mannitol did not.

After rapid dialysis with glycerol (group 5), changes in arterial blood gases were similar to those observed after dialysis with standard dialysate. In CSF, however, the pH was 7.30 ± 0.02 (predialysis value, 7.29 ± 0.03), and bicarbonate concentration was 18.5 ± 0.8 mmoles/liter (predialysis value, 18.8 ± 0.6). Thus, addition of glycerol to dialysate prevented the fall in the pH of CSF observed after standard hemodialysis.

Changes in brain intracellular pH. In uremic dogs (group 2), the intracellular pH (pH1) of brain was 7.06 ± 0.02 in gray matter (normal, 7.05 ± 0.01) and 6.97 ± 0.01 in white matter (normal, 6.98 ± 0.02). After rapid dialysis with standard dialysate (group 3), the pH1 in cerebral cortex had fallen to 6.89 ± 0.02 (P < 0.01) while that in white matter was unaltered (7.00 ± 0.06) (Fig. 1). Accompanying the fall in pH1 of cerebral cortex was a 10% increase in its water content (Fig. 2), without significant change in brain content of magnesium, potassium, or chloride (Fig. 3). There was a decrement in calcium and a rise in sodium concentrations (Fig. 3).

After rapid dialysis with mannitol (group 4), the pH1 of cerebral cortex was 7.02 ± 0.04, a value not significantly different from normal or uremic animals (P > 0.05 vs. groups 1 and 2) but significantly greater than observed after rapid dialysis with standard dialysate (P < 0.01 vs. group 3). The pH1 of white matter remained in the normal range (7.05 ± 0.04). Thus, addition of mannitol to the dialysate also prevented the fall in brain pH1 induced by rapid hemodialysis (Fig. 1).

Rapid dialysis with glycerol added to dialysate significantly modified the changes in brain pH1. After hemodialysis with glycerol (group 5), the pH1 of cerebral cortex was 7.14 ± 0.01 (P < 0.01 vs. uremic animals treated with rapid hemodialysis, Fig. 1), although that in white matter was unaltered (7.00 ± 0.03). The cerebral cortex pH1 was essentially unchanged 4 hr after dialysis (7.15 ± 0.02), as
Brain tissue (cerebral cortex) content of potassium, sodium, calcium, and magnesium in five groups of dogs. Brain calcium concentration is significantly elevated ($P < 0.01$) in uremic animals and is restored to normal by dialysis (groups 3 through 5). Brain sodium concentration is significantly decreased in uremic dogs (group 2) and is restored to normal by dialysis (group 3) or dialysis with glycerol (group 5), but not with mannitol (group 4). Brain magnesium and potassium concentrations are unaffected by uremia or dialysis.

was that in white matter ($7.01 \pm 0.04$). Thus, dialysis with glycerol prevented the fall in brain pH observed after rapid dialysis (Fig. 1).

**Brain osmolality.** In uremic dogs, the brain osmolality was $342 \pm 10$ mOsm/kg of water (normal, $305 \pm 5$). After hemodialysis with mannitol in the dialysate (group 4), brain osmolality was $334 \pm 7$ mOsm/kg of water, which was also similar to values observed in plasma ($342 \pm 4$ mOsm/kg) and CSF ($335 \pm 4$ mOsm/kg). After hemodialysis with glycerol (group 5), brain osmolality was $335 \pm 8$ mOsm/kg of water, a value not different from osmolalities of plasma ($339 \pm 4$ mOsm/kg) or CSF ($340 \pm 2$ mOsm/kg). Four hours after cessation of dialysis (group 6), brain osmolality was $326 \pm 6$ mOsm/kg of water.

The brain osmole content after hemodialysis with glycerol was $1,350 \pm 29$ mOsm/kg of dry wt (normal, $1242 \pm 34$), a value not different from that observed after rapid hemodialysis with mannitol ($1336 \pm 31$ mOsm/kg of dry wt) or in uremic animals not treated with hemodialysis ($1371 \pm 20$ mOsm/kg of dry wt). After rapid hemodialysis with standard dialysate (group 3), however, the brain osmole content was $1,444 \pm 27$ mOsm/kg of dry wt, a value significantly higher ($P < 0.05$) than that observed after dialysis with either glycerol or mannitol added to the dialysate (groups 4 and 5). The difference in osmole content between groups 4 and 5, vs. group 2, presumably represents idiogenic osmole formation by the brain. Thus, rapid dialysis with either glycerol or mannitol in the dialysate prevented the formation of idiogenic osmoles by the brain.

**EEG changes.** In dogs with acute renal failure (group 2), the EEG was grossly abnormal, as shown in Figures 4 and 5. The percent EEG power $< 5$ Hz was $44 \pm 5\%$, vs. the normal value of $4.4 \pm 1.4\%$ ($P < 0.01$). The percent of frequencies $> 9$ Hz (normal frequencies) was only $10 \pm 3\%$ (normal, $57 \pm 7\%, P < 0.01$), although frequencies $< 7$ Hz (generally abnormal frequencies) were $66 \pm 4\%$ (normal, $17 \pm 4\%, P < 0.01$).

Both during and after rapid hemodialysis (group 3), there was no significant alteration in any of the aforementioned EEG measurements (Figs. 4 and 5). Similarly, during and after rapid hemodialysis with mannitol (group 4), there was also no significant alteration in either the percent of EEG power $< 5$ Hz, or the frequency distribution above $9$ Hz or below $7$ Hz (Figs. 4 and 5).
There were significant shifts in the EEG after rapid dialysis with glycerol. The percent of EEG power < 5 Hz was 8.6 ± 2.2%, a value not different from normal (Fig. 4). Both the percent of EEG frequencies below 7 Hz (27 ± 6) and above 9 Hz (39 ± 6) improved (Fig. 5), and were not significantly different (P > 0.05) from normal values. Four hours after rapid dialysis with glycerol, the percent of EEG power < 5 Hz (10.4 ± 2.4%) and the percent of EEG frequencies below 7 Hz (33 ± 8%) were not different from normal values (P > 0.05). The percent of EEG frequencies > 9 Hz (31 ± 8%) were significantly (P < 0.05) below normal. Thus, rapid dialysis with glycerol in the dialysate improved the EEG almost to normal, and most of these changes persisted for at least 4 hr after the termination of dialysis.

Brain water and electrolytes. After rapid dialysis of uremic dogs, there were significant increases of brain tissue water content in both white and gray matter (Fig. 2). The water content in white matter was 237 ± 12 g/100 g of dry wt (uremia, 211 ± 6), and that in gray matter was 460 ± 11 g/100 g of dry wt (uremia, 397 ± 7). After rapid dialysis with glycerol (group 5), however, brain water was normal in both white (208 ± 9 g/100 g of dry wt) and gray (402 ± 10 g/100 g of dry wt) matter (Fig. 2). Four hours after termination of dialysis (group 6), brain water content remained within the normal range of both gray (417 ± 6 g/100 g of dry wt) and white (195 ± 2 g/100 g of dry wt) matter. After rapid dialysis with mannitol (group 4), brain water content was also normal in both white (205 ± 3 g/100 g of dry wt) and gray (406 ± 9 g/100 g of dry wt) matter (Fig. 2). Thus, rapid dialysis with either glycerol or mannitol added to the dialysate prevented the development of brain edema.

In animals with acute renal failure (group 2), there was a significant decrease in brain tissue (cerebral cortex) content of sodium (Fig. 3). After dialysis with either standard dialysate or glycerol (groups 3 and 5), brain sodium concentration increased to normal values (Fig. 3). Brain potassium and magnesium content were essentially unaltered by either uremia or dialysis (Fig. 3). Cerebral cortex calcium concentration was 19.6 ± 1.1 mEq/kg of dry wt in uremic animals (normal value, 13.2 ± 0.5, P < 0.01). After dialysis (groups 3), brain calcium concentration decreased towards normal to 15.2 ± 0.8 mEq/kg of dry wt. After dialysis with glycerol or mannitol (groups 4 and 5), cerebral cortex calcium concentration content also decreased to 14.2 ± 0.7 and 15.4 ± 0.8 mEq/kg of dry wt, respectively (Fig. 3).

Discussion

These experiments demonstrate that in acutely uremic dogs treated with hemodialysis, experimental dialysis disequilibrium syndrome can be prevented by addition of glycerol to the dialysate. Additionally, many of the manifestations of experimental DDS are also prevented by addition of mannitol to dialysate.

The manifestations of experimental DDS consist of brain edema due to an osmotic gradient from brain to plasma [6, 7], with a fall in pH of CSF and pH1 in cerebral cortex [8] and an abnormal EEG [3, 4, 23, 24]. The elevated brain osmolality is not due to retention in brain of commonly measured solutes, such as sodium, potassium, chloride, calcium, magnesium, urea, or lactate [6—8], but appears rather to be due to the de novo generation in brain of unidentified solutes—idiogenic osmoles [6, 8].

Production of the idiogenic osmole appears to be related to the fall in pH of CSF and cerebral cortex pH1 [8]. In the present experimental model of DDS, these pH decrements occurred even though animals were mechanically ventilated, with arterial Pco2 maintained constant throughout the experiment. Another group where there is an apparent pH disequilibrium between CSF and arterial blood is patients with diabetic ketoacidosis who are rapidly given i.v. sodium bicarbonate. In this situation, there is apparent hypoventilation, with a rise in arterial Pco2, diffusion of carbon dioxide into the CSF, and a resultant fall in pH of CSF [25—27]. The situation is apparently different, however, in patients with renal failure. Here, plasma bicarbonate concentration is rapidly elevated by infusion (across the dialysis membrane) of acetate, with subsequent conversion to bicarbonate. Studies of acid-base status in uremic subjects treated with hemodialysis, however, suggest that despite acute elevation of plasma bicarbonate concentration, hypoventilation is not generally observed [23, 28]. In animal studies reported here and elsewhere [6, 8], brain pH1 and pH of CSF fall during hemodialysis although arterial Pco2 is unaltered. It appears that both the fall in brain pH1, as well as the pathogenesis of DDS, are unrelated to changes in arterial Pco2.

It has also been observed that at the start of a high efficiency hemodialysis, there may be an initial rapid removal of bicarbonate via the dialysis membrane, with delayed conversion of acetate to bicarbonate resulting in a transitory worsening of metabolic acidosis [29]. Such rapid alterations in arterial pH may result in systemic manifestations sim-
ilar to DDS. The symptoms may be partially alleviated by substitution of bicarbonate for acetate in the dialysate. The systemic effects of high efficiency dialysis with acetate may actually be due to acetate intolerance in selected patients. In general, acute metabolic alterations of blood pH do not affect brain intracellular pH [30]. Also, a sudden fall in plasma bicarbonate concentration during dialysis was not observed in the present experiments. This may reflect either relatively infrequent sampling of arterial blood (each 30 min) or more efficient metabolism of acetate in the dog. Thus, the observed effects of rapid dialysis on brain pH in the present studies appear to be separate from any changes in arterial pH. Both glycerol and mannitol added to the dialysate prevent the fall in brain pH (Fig. 1), and as a result, idiogenic osmoles are not present in the brain of animals so treated.

After rapid dialysis with glycerol, intracellular pH of brain is slightly alkalotic (Fig. 1). Intracellular alkalosis has previously been noted in association with hyperosmolality [31]. Although the exact mechanism is unclear, intracellular alkalosis may be associated with an acceleration of glycolysis [31]. With increased availability of glycerol, there should be increased dihydroxyacetone phosphate [32], with subsequent increased production of lactate.

Each mole of lactate metabolized consumes one mole of hydrogen ion, thereby generating a mole of bicarbonate. Both hyperosmolality and glycerol infusion can result in intracellular alkalosis [31, 33], and both may also be associated with increased lactate production [32, 34] via accelerated glycolysis. The increased glycolysis may become self-perpetuating, as intracellular alkalosis would then tend to accelerate activity of many glycolytic enzymes [32]. Since brain metabolic rate is decreased in uremia [35, 36], acceleration of glycolysis, with increased utilization of adenosine triphosphate, also may be related to the central nervous system effects noted after dialysis with glycerol, but not with mannitol.

Glycerol has been shown to be an effective cerebral dehydrating agent, both in normal animals and in those with experimental brain edema [12, 13]. In addition, glycerol has been used extensively in patients to treat cerebral edema due to numerous causes [9–11, 15–17]. Although its mode of action may be largely mediated by its osmotic effects, glycerol also has been shown to increase cerebral blood flow [17]. In addition, it has also been suggested that glycerol may somehow act to increase oxidative phosphorylation in brain [15–17], possibly by its conversion to alpha-glycerophosphate and then to dihydroxyacetone phosphate which can enter the Embden-Meyerhof glycolytic pathway. This assumption, however, has not been validated. That glycerol may have other than an osmotic effect on brain is suggested by comparing its effects on brain to that of other osmotically active agents. When added to dialysate during rapid dialysis of uremic dogs, either sodium chloride, urea, or mannitol will prevent brain edema [6] (Fig. 2). Only glycerol, however, prevents the fall in pH of CSF and improves the EEG (Figs. 1, 4, and 5).

We find (Figs. 4 and 5) that there is no change in the EEG after rapid hemodialysis with standard dialysate. These results may initially appear to be in conflict with results from other studies where the EEG is reported to deteriorate following dialysis with standard dialysate [3, 4, 23, 24]. Evaluation of these reports shows that in no instance was a systematic evaluation of the EEG performed. Rather, short segments of the EEG are shown, and there are no standardized criteria used for evaluating or quantitating deterioration of the EEG. Even under such circumstances “deterioration” of the EEG is not seen in all patients [24], and the changes observed are well within the expected range for patients with renal failure itself, not treated with dialysis [37–39]. There may well be sporadic abnormal bursts in the EEG during dialysis [4, 23, 40], but the overall pattern of the tracing is essentially unaltered (Figs. 4 and 5). It should be pointed out, however, that our evaluation of the EEG does not take into account possible effects on visually evoked cortical potentials [41], discriminant analysis [42], or photic driving [41]. These parameters may become transiently abnormal during dialysis [40].

There are several studies in uremic patients where effects of various hyperosmolar substances added to the dialysate are evaluated. Such substances include urea, glucose, fructose, sodium chloride, and mannitol [23, 24, 43–49]. All of these reports are difficult to evaluate, as the factors examined were generally subjective clinical symptoms, and different symptoms were studied in different reports. The effects on these symptoms are inconsistent from one report to the next [4]. Additionally, many of the patients studied had stable chronic renal failure and were being treated with maintenance hemodialysis. Such patients are highly unlikely to develop DDS under any circumstances [4]. It does appear that in uremic patients being treated with hemodialysis, addition of either sodium chloride or mannitol to dialysate may partially ameliorate some of the symptoms associated with DDS [24, 47–49].
Because of their tendency to accumulate in the body between dialysis and the dangers of circulatory congestion and hypertension, neither of these agents, however, would appear to be satisfactory for routine use, and certainly not on a repetitive basis.

Glycerol, on the other hand, has a half-life of less than 3.5 hr in anephric animals [12] and is not toxic in doses commonly employed [10, 12]. Glycerol may thus be a suitable agent for prevention of dialysis disequilibrium in man.

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