Central Nervous System pH in Uremia and the Effects of Hemodialysis

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ABSTRACT Rapid hemodialysis of uremic animals may induce a syndrome characterized by increased cerebrospinal fluid (CSF) pressure, grand mal seizures, and electroencephalographic abnormalities. There is a fall in pH and bicarbonate concentration in CSF, and brain osmolality exceeds that of plasma, resulting in a net movement of water into the brain. This syndrome has been called experimental dialysis disequilibrium syndrome. The fall in pH of CSF may be secondary to a fall of intracellular pH (pHi) in brain. Since changes in pHi can alter intracellular osmolality in other tissues, it was decided to investigate brain pH in uremia, and the effects of hemodialysis. Brain pH was measured by evaluating the distribution of 4C-labeled dimethadione in brain relative to CSF, while extracellular space was calculated as the 4SO4 space relative to CSF. In animals with acute renal failure, brain (cerebral cortex) pH was 7.06±0.02 (±SE) while that in CSF was 7.31±0.02, both values not different from normal. After rapid hemodialysis (100 min) of uremic animals, plasma creatinine fell from 11.8 to 5.9 mg/dl. Brain pH was 7.19±0.02, both values significantly lower than in uremic animals (P < 0.01), and there was a 12% increase in brain water content. After slow hemodialysis (210 min), brain pH (7.01±0.02) and pH in CSF (7.27±0.02) were both significantly greater than values observed after rapid hemodialysis (P < 0.01), and brain water content was normal. None of the above maneuvers had any effect on pH of skeletal muscle or subcortical white matter.

The data show that rapid hemodialysis of uremic dogs is accompanied by a significant fall in pH of CSF and pHi in cerebral cortex. Accompanying the fall in brain pH, pHi is cerebral edema.

INTRODUCTION

Dialysis disequilibrium syndrome (DDS) is a well described complication of the treatment of renal failure with hemodialysis (1, 2). The syndrome is most common either in patients undergoing their initial treatment with hemodialysis or in children (3). The usual symptoms of DDS are headache, nausea, restlessness, and lethargy, while seizures and coma may occur (1, 2). In patients with DDS, the electroencephalogram usually shows a characteristic pattern (4) and there is often a fall in pH of cerebrospinal fluid (CSF) both in man (5, 6) and experimental animals (7). We have previously shown that when acutely uremic dogs (bilateral ureteral ligation for 37 days) are treated with rapid hemodialysis (blood flow = 12 ml/kg per min for 100 min), they may develop experimental DDS. In such animals, there is an osmotic gradient from brain to plasma that results in a net movement of water into brain. The osmol content of brain in animals treated with rapid hemodialysis was significantly greater than that of animals treated with slow hemodialysis (blood flow = 5 ml/kg per min for 210 min), although plasma urea, creatinine, and osmolality fell by the same amount after either dialytic procedure (7). The increased brain osmol content could not be entirely accounted for by changes in brain concentration of Na+, K+, Cl−, Ca++, Mg++, or urea (7, 8).

Along with the increase in brain osmol content, a significant fall in both pH and bicarbonate concentration...
Normal, n = 8
Mean 7.31 — 41 — 67 — 19.6 — 2.2 — 7.36 — 36 — 77 — 20.6
±SE 0.01 — 1 — 6 — 0.7 — 0.2 — 0.01 — 1 — 6 — 0.8

Uremic, n = 8
Mean 7.31 — 41 — 48* — 19.7 — 2.4 — 7.22* — 34 — 83 — 13.5*
±SE 0.02 — 1 — 4 — 0.7 — 0.3 — 0.02 — 1 — 6 — 0.8

Uremic + slow hemodialysis, n = 5
Mean 7.30 7.27 40 42 55 56 19.6 18.2 2.6 7.23* 7.33 36 37 76 72 14.6* 18.9
±SE 0.01 0.02 3 2 3 3 0.8 0.4 0.4 0.02 0.02 2 2 6 5 0.7 1.3

Uremic + rapid hemodialysis, n = 7
Mean 7.33 7.19* 37 43* 55 55 18.9 15.4* 2.2 7.21* 7.31* 35 36 78 74 13.7* 17.7*
±SE 0.02 0.02 2 3 4 3 1.1 0.5 0.2 0.04 0.01 3 1 4 6 1.0 0.7

I, initial sample, before hemodialysis; F, final sample, after hemodialysis.
* P < 0.01 versus normal animals.

n = number of animals.

of CSF is observed in animals treated with rapid hemodialysis (7). The CSF has thus undergone a net gain in H+ ion. These H+ ions could have come from only two places—blood or brain. Since arterial pH rose while that of CSF fell, it is most likely that the increased H+ ion in CSF came from the brain.

The gain of H+ ions by CSF thus suggests a possible fall in intracellular pH (pHi) of the brain in uremic animals treated with rapid hemodialysis. It has been demonstrated that a fall in pH can increase intracellular osmolality in other cell systems, particularly the red blood cells (9). Rapid hemodialysis in some manner may result in a decrease of brain pHi, with a resultant increase in intracellular osmolality in brain. Such a sequence could account for many of the observed manifestations of experimental DDS. It is the purpose of the present experiments to evaluate pHi of brain in uremic animals, and the effects of both rapid and slow hemodialysis.

METHODS

Studies were done in four groups of mongrel dogs of both sexes, 18-26 kg, as follows: (a) normal animals; (b) dogs with acute uremia of 3½ days duration; (c) acutely uremic dogs treated with rapid hemodialysis; (d) acutely uremic dogs treated with slow hemodialysis. Groups contained five to eight animals.

In all animals, measurements were made in CSF and arterial blood or plasma of pH, Pco2, Pao2, bicarbonate, osmolality, urea, creatinine, and radioactivity from [4-dione-2-14C]5,5-dimethyloxazolidine-2 (14C]DMO) and 35SO4. Both isotopes are from New England Nuclear, Boston, Mass. Lactate was measured both in CSF and in a portion of the cerebral hemisphere rapidly (less than 5 s) frozen in liquid nitrogen.

Acute uremia was induced by bilateral ureteral ligation for 3½ days, at which time plasma urea and creatinine were 65.8 mM and 11.8 mg/dl, respectively. Hemodialysis was carried out with a Travenol RSP unit pediatric coil with 0.6 M2 surface area at a dialysate flow rate of 500 ml/min (Travenol Laboratories, Artificial Organs Div., Morton Grove, Ill.). Blood flow for rapid hemodialysis was 12 ml/kp per min for 100 min, and for slow hemodialysis, 5 ml/kg per min for 210 min, employing standard dialysate (Diasol, Travenol Laboratories, Deerfield, Ill.). The techniques have previously been described (7).

All animals were studied while under anesthesia (sodium pentobarbital 25 mg/kg i.v.), intubated, and mechanically ventilated while spontaneous respiration was controlled with i.v. succinyl choline, as previously described (7, 10). After intubation, the arterial Pco2 was adjusted to about 35 mm Hg and animals were then given both [14C]DMO, 8 µCi/kg i.v. and 0.1 µCi/kg in the cisterna magna, and Na2SO4, 20 µCi/kg i.v. and 2.5 µCi/kg into the cisterna magna. The techniques have previously been described (10). The [14C]DMO was dissolved in 0.4 M "cold" DMO at a concentration of 25 µCi/ml while the Na2SO4 was in 100 mM "cold" Na2SO4 at a concentration of 50 µCi/ml. The pH and extracellular space were determined in muscle, gray matter, and white matter by evaluating the distribution of both DMO and 35SO4 relative to either cortical CSF or plasma; the complete analytical method has been described (10). Briefly, after injecting the isotopes as described above, a 3-h equilibration period was allowed. At the conclusion of the experiment, samples were obtained of both cisternal and cortical CSF, arterial blood, skeletal muscle, brain subcortical white matter, brain cortical gray matter, and cerebral hemisphere, as previously described (7). Triplicate samples, each about...
TABLE II

Changes of Intracellular pH in Brain and Skeletal Muscle

<table>
<thead>
<tr>
<th></th>
<th>Gray matter</th>
<th>White matter</th>
<th>Muscle</th>
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<tbody>
<tr>
<td></td>
<td>pH</td>
<td>ECS</td>
<td>Lactate</td>
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<tr>
<td>Normal, n = 8</td>
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<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>7.05</td>
<td>21.9</td>
<td>2.6</td>
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<tr>
<td>±SE</td>
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<td>2.4</td>
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<tr>
<td>Uremia, n = 8</td>
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</tr>
<tr>
<td>Mean</td>
<td>7.06</td>
<td>21.0</td>
<td>2.9</td>
</tr>
<tr>
<td>±SE</td>
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<td>2.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Uremia + slow hemodialysis, n = 5</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>7.01</td>
<td>22.9</td>
<td>1.9</td>
</tr>
<tr>
<td>±SE</td>
<td>0.02</td>
<td>3.8</td>
<td>0.1</td>
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<tr>
<td>Uremia + rapid hemodialysis, n = 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>6.89*</td>
<td>17.3</td>
<td>2.6</td>
</tr>
<tr>
<td>±SE</td>
<td>0.02</td>
<td>3.2</td>
<td>0.2</td>
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</tbody>
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* P < 0.01 vs. normal or uremic animals, or uremic animals treated with slow hemodialysis. ECS = extracellular space; n = number of animals.

0.1 g of the outer 0.4 mm of cerebral cortex and of subcortical white matter 0.8-1.2 mm below the brain surface were obtained with a special tissue slicer (11). The samples of brain and muscle (each about 0.4 g) were extracted with 0.5 M perchloric acid as previously described (11). Duplicate aliquots of supernate, plasma, and cortical CSF were treated with BaCl₂ to precipitate SO₄²⁻ but retain C. All samples were counted as previously described (11, 12). Subtracting ¹⁴C activity from the total radioactivity gave the counts due to SO₄²⁻ (12). The pH was measured in both arterial and cisternal CSF (10). Brain gray matter extracellular space was calculated as the ratio of radioactivity per gram tissue to radioactivity per gram CSF. The intracellular pH was calculated by the distribution of [¹⁴C]-DMO in tissue relative to cortical CSF (for gray matter) or plasma H₂O (for white matter or muscle). The formula was modified from that described by Kibler et al. (13), with pH of cisternal CSF for gray matter and arterial pH for muscle and white matter. The bicarbonate concentration in cerebral cortex was calculated from values for cerebral cortex pH and Pco₂ of CSF, as described by Kjällquist et al. (14). Measurements of urea, creatinine, osmolality, pH, Pco₂, bicarbonate, and Pco₂ were made in CSF and arterial blood by previously described methods (7, 10), and lactate was measured in CSF and brain (10).

RESULTS

The normal values for CSF and arterial blood pH, Pco₂, bicarbonate, and lactate are shown in Table I, while control values for pH of muscle, gray matter, and white matter are in Table II. In the acutely uremic dogs, plasma osmolality (±SE) was 347±6 mosmol/kg, while plasma urea and creatinine were 65.8±0.4 mM and 11.8±0.4 mg/dl, respectively. In animals with acute renal failure, despite a fall in arterial pH from 7.36 to 7.22, there was no change in the pH of either brain or muscle (Fig. 1). Both the pH and bicarbonate in CSF were normal (Table I), despite the significant fall in plasma bicarbonate concentration.

Dogs were then treated with either rapid or slow hemodialysis. After rapid hemodialysis, plasma urea and creatinine fell to 24.4±2.4 mM and 6.4±0.5 mg/dl, respectively. There was no change in the pH of skeletal muscle. However, there was a highly significant fall (P < 0.001) in the pH of brain (Fig. 2). The pH in
cerebral cortex was 6.89±0.02 (±SE), versus 7.06±0.02 \( (P < 0.01) \) observed in uremic animals. There was a fall in cerebral cortex bicarbonate to 8.0±0.5 mmol/kg H2O (normal value, 11.3±0.4 mmol/kg H2O) but no change in brain lactate (Table II). Accompanying the fall in gray matter pH i was a significant \( (P < 0.01) \) fall in pH of CSF (Fig. 3), from 7.33±0.02 before dialysis to 7.19±0.02 after \( (P < 0.001) \), while CSF bicarbonate fell from 18.9±1.1 mmol/liter to 15.4±0.5 mmol/liter \( (P < 0.001) \), and lactate in CSF was unaltered (Table I). In addition to the fall in cerebral cortex pH i, there was also cerebral edema, as defined by an increase in brain water content from 397±7 to 442±15 g/100 g dry wt \( (P < 0.01) \) in cerebral cortex and 211±6 to 237±9 g/100 g dry wt in white matter \( (P < 0.01) \).

After dogs were treated with slow hemodialysis for 210 min, plasma urea and creatinine fell by an amount similar to that after rapid hemodialysis. The cerebral cortex pH i fell slightly to 7.01±0.02, not different from normal \( (P > 0.09) \), but significantly greater \( (P < 0.003) \) than the brain pH i observed after rapid hemodialysis (Fig. 2). Both the bicarbonate and pH of CSF in dogs treated with slow hemodialysis (18.2±0.4 mmol/liter and 7.27±0.02) were significantly different from values observed after rapid hemodialysis \( (P < 0.01) \). Animals treated with slow hemodialysis did not develop brain edema (Table II). The pH i in brain white matter did not change after either rapid or slow hemodialysis (Table II).

**DISCUSSION**

The data presented suggest that in acutely uremic animals treated with rapid hemodialysis, there is a significant increase in brain H+ ion activity. The increase in H+ ion is accompanied by an increase in brain osmole content (7), leading to an increase in brain water content. Brain H+ ion is increased by a significantly lesser increment when uremic animals are treated with slow hemodialysis. The source of the increased brain H+ ion is not known, but it is probably not due to hypoxia, decreased cerebral blood flow, or increased cerebral lactate production. Cerebral hypoxia is unlikely, as the Po2 in CSF was normal and Po2 of CSF is similar to that of brain (15, 16). Furthermore, cerebral hypoxia should lead to increased brain lactate, and such a phenomenon did not occur (Table II). Similarly, decreased cerebral blood flow probably did not occur, as such a circumstance should lead to a fall in Po2 of CSF, and an increase in brain and CSF lactate (15). In animals treated with rapid hemodialysis, brain and CSF lactate were normal (Tables I and II). Although the exact biochemical sequence leading to an increase in brain H+ ion is not known, rapid hemodialysis of uremic animals may lead to an increase in brain organic acid(s). In both mammals (17, 18) and amphibians (19) in whom abrupt increases in extracellular osmolality are induced, brain content of amino acids increases. In primates subjected to reversible asphyxia, there is an increase in brain glutamic acid, probably a result of increased conversion from glutamine (20). The presence in brain of strong organic acid(s) would tend to increase osmolality by at least two mechanisms: (a) displacement of intracellularly bound K+ ion from protein anions by H+ ions, as in the hemoglobin molecule (9, 20); the K+ ion, osmotically inactive when bound to intracellular protein, may become osmotically active when displaced by a H+ ion. (b) Production of increased quantities of organic acids, per se, could raise brain osmolality.
The water content increased in both gray and white matter of the brain (Table II), although pHf fell only in gray matter. Why pHf did not fall in white matter is not entirely clear, but may be related to the different structural characteristics of the two tissues. White matter consists largely of myelin and fibers, containing little cellular material, while gray matter is largely cellular. The method used to evaluate pHf (10) may not be sufficiently sensitive when only a small portion of the tissue actually consists of cells. The actual increase in white matter water content was less than that observed in gray matter (Table II).

In patients with metabolic acidosis from various causes, it has been shown that when arterial pH is rapidly corrected by infusion of NaHCO3, a paradoxical acidosis may develop in the CSF (16). The fall in pH of CSF is essentially all due to a rise in PCO2 of CSF, secondary to hypoventilation induced by rapid elevation of arterial pH and bicarbonate. In patients with subacute metabolic acidosis, both pH and PCO2 tend to be abnormally low in CSF. Because of the blood-brain barrier, when plasma bicarbonate is elevated with intravenously administered NaHCO3, plasma and CSF bicarbonate levels will not equilibrate for several hours, while PCO2 equilibrates within minutes (21, 22). Thus, when hypoventilation results in a rise of arterial PCO2, the pH in CSF will fall as CO2 rapidly diffuses into the CSF (21–23).

In 18 patients with diabetic ketoacidosis in whom pH of CSF was evaluated during therapy (22–24), pH of CSF fell from 7.30 to 7.20 while arterial pH rose from 7.08 to 7.34. However, the fall in pH of CSF was entirely due to a rise in CSF PCO2 (from 24 to 34 mm Hg), as bicarbonate in CSF actually rose slightly (from 10.9 to 12.1 mmol/liter).

The situation during hemodialysis is quite different. Arterial pH is rapidly elevated as a consequence of intravenous administration (through the dialysis membrane) of bicarbonate precursor (lactate or acetate). However, studies of acid-base status in uremic patients treated with dialysis suggest that despite rapid elevation of arterial pH and bicarbonate, hypoventilation is not generally observed (25). In animal studies reported here and elsewhere (7), pH of CSF fell during hemodialysis although arterial PCO2 was maintained at a constant level (Table I).

However, the fall in pH of CSF was primarily due to a fall in CSF bicarbonate (Table I), implying the de novo presence of organic acids. Thus, the production of paradoxical CSF acidosis after rapid hemodialysis is not related to systemic hypoventilation and is a different mechanism from that observed after treatment of other forms of metabolic acidosis (22–24, 26, 27).

Whatever the mechanisms, rapid hemodialysis of uremic animals results in a fall in pH of CSF and cerebral cortex pHl, associated with increased brain osmole content and cerebral edema. There is a concomitant fall in pH and bicarbonate concentration of CSF, but no change in skeletal muscle pHl, while pH and bicarbonate of arterial blood rise. This phenomenon appears to be a major mechanism in the pathogenesis of DDS in experimental animals.

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REFERENCES


A. I. Arieff, R. Cuisado, S. G. Massry and V. C. Lazarowitz


