Sodium Modeling Ameliorates Intradialytic and Interdialytic Symptoms in Young Hemodialysis Patients

Robert H. Sadowski, Elizabeth N. Allred, and Kathy Jabs

R.H. Sadowski, K. Jabs, Division of Nephrology, Children's Hospital and Harvard Medical School, Boston, MA
E.N. Allred, Neuroepidemiology Unit, Children's Hospital, Boston, MA
(J. Am. Soc. Nephrol. 1993; 4:1192–1198)

ABSTRACT
Despite advances in the delivery of hemodialysis, significant dialytic morbidity persists. Sodium modeling in older adults has been shown to decrease some dialytic symptoms, but clear benefits in young patients without coexisting diabetes or advanced cardiovascular disease have not been shown. The effects of sodium modeling were evaluated in 16 adolescent and young adult hemodialysis patients (16 to 32 yr of age) treated with conventional hemodialysis for a median of 11.5 months. The 8-wk study was divided into four 2-wk blocks. During each block, one of three sodium programs or a constant (control) dialysate sodium of 138 mEq/L was used. During each sodium program, the initial dialysate sodium of 148 mEq/L was decreased by an exponential, linear, or step program to 138 mEq/L. Treatments with sodium modeling were significantly better than those with constant sodium dialysate. When all sodium programs were grouped and compared with constant dialysate sodium, the odds of improvement in dialytic cramps, headaches, and nausea were 1.8, 2.1, and 3.9, respectively (P < 0.05). Sodium modeling also significantly decreased the frequency of postdialysis hypotension and interdialytic fatigue, dizziness, and muscle cramping (P < 0.05). No differences were seen among the sodium protocols in the incidence of symptomatic hypotension, the amount of normal saline administered, the degree of volume concentration during treatments, or the decrease in serum osmolality. There was no increase in pretreatment or posttreatment serum sodium concentrations, interdialytic thirst, weight gain, or hypertension. Sodium modeling dramatically decreases both intradialytic and interdialytic morbidity in young hemodialysis patients. There was no increase in adverse events associated with sodium modeling.

Key Words: Sodium modeling, hemodialysis, hypotension, dialysate, sodium variation

Despite improvements in the techniques of hemodialysis, treatments continue to be complicated by hypotension, muscle cramps, headaches, nausea, vomiting, and fatigue (1–3). Although the physiologic mechanisms responsible for dialytic morbidity have not been completely elucidated, rapid fluid shifts and osmotic gradients between intracellular and extracellular compartments are likely contributors. During ultrafiltration, fluid is initially removed from the intravascular compartment. If the ultrafiltered fluid is not promptly "refilled" by fluid from the extravascular space, hypotension and cramping may result (4–8). In addition, lowering the extracellular osmolality may result in a transient osmotic gradient between the extracellular and intracellular spaces with resultant cell swelling. In the central nervous system, this sequence of events is thought to play a role in the genesis of the "dialysis disequilibrium" symptoms of headache, nausea, and vomiting (1,9).

Over the last 20 yr, a number of approaches have been used to alleviate intradialytic symptoms. Most strategies have been directed at preserving intravascular volume and minimizing osmotic gradients between fluid compartments. These strategies have included sequential ultrafiltration-hemodialysis (10), sequential changes in the dialysate sodium concentration during treatments (11,12), dialysis with a constantly high dialysate sodium concentration (13–17), and more recently, the use of sodium modeling (18,19).

Sodium modeling is a programmed means of varying the dialysate sodium concentration during a dialysis treatment. Most currently used sodium programs begin the dialysis treatment with a hyperosmolar dialysate sodium concentration. The resultant increase in serum sodium concentration during the
early portion of the dialysis treatment is intended to offset the decrease in osmolality caused by the removal of urea and other small solutes. During the treatment, the dialysate sodium concentration is decreased by the proportionate dilution of the dialysate to isosmolar levels (approximately 138 mEq/L) in a pattern determined by the individual sodium program. The goal of most sodium programs is the return of the patient's serum sodium concentration to a low-normal level at the conclusion of the treatment.

Sodium modeling has been shown to reduce dialytic morbidity in older adult patients receiving high-flux hemodialysis (19); however, the efficacy of sodium modeling in young hemodialysis patients is unknown. In addition, the relative benefits and risks of the various sodium programs have not been delineated. The purpose of this study was to examine the effects of sodium modeling in young hemodialysis patients whose hemodynamic status was not affected by long-standing diabetes mellitus or cardiovascular disease. Indeed, younger patients, without the long-term vascular and hemodynamic consequences of diabetes or chronic hypertension, may be the best population to delineate the effects of sodium modeling. An additional goal was to determine if individual sodium programs selectively alleviated particular symptoms.

METHODS

Subjects

Patients at the Children's Hospital Renal Dialysis Unit who had been receiving maintenance hemodialysis for at least 1 month and who were medically stable were eligible for enrollment. Sixteen of the 18 eligible patients completed the 8-wk study. Two patients were withdrawn from the study: one underwent cadaveric renal transplantation, and one had a prolonged hospitalization for sepsis.

The patients enrolled in the study were 16 to 32 yr of age (median, 19 yr) and developed ESRD as a result of obstructive or reflux nephropathy (6), renal dysplasia or hypoplasia (2), or chronic glomerulonephritis (8). No patient had renal failure as a result of diabetes mellitus or chronic hypertension. Six patients were anephric. Five patients required antihypertensive medications before and during the study period, including β-blockers, converting enzyme inhibitors, and calcium channel blockers. The patients had been receiving maintenance hemodialysis for 1 to 144 months (median, 11.5 months).

The patients underwent conventional dialysis with 0.7- to 1.3-m² hollow-fiber polysulfone dialyzers and blood flows of 300 to 400 mL/min on Fresenius 2008 machines (Fresenius USA, Inc., Seratronics, Inc., Concord, CA). The dialysis times of 1.5 to 3 h were determined by standard urea kinetic modeling with Kt/V values of 1.29 ± 0.25 (mean ± SD). Bicarbonate-based dialysate was delivered at 500 mL/min. Ultrafiltration was performed at a constant rate with the patient's estimated dry weight as the ultrafiltration goal.

Study Design

The study design was approved by the Committee on Clinical Investigation at Children's Hospital, and informed consent and assent were obtained from all study participants or their parents. The 8-wk study period was divided into four 2-wk blocks. Each time block consisted of six consecutive hemodialysis treatments. During three of the time blocks, a different sodium program (exponential, linear, or step) was used (Figure 1). The initial dialysate sodium concentration was 148 mEq/L. The dialysate sodium concentration was decreased in a linear or exponential fashion over the entire treatment in the linear and exponential programs, respectively, to a final concentration of 138 mEq/L. In contrast, during the step program, the dialysate sodium was maintained at 148 mEq/L for the majority of the treatment and was then abruptly decreased to 136 mEq/L for the final 30 min. During the fourth 2-wk block, the dialysate sodium concentration was held constant at 138 mEq/L throughout each treatment. This time block served as a control period for each patient. The same dialysate sodium protocol was used for all six treatments during a 2-wk time block. The order of the sodium programs was random, and patients were blinded to the sodium protocol in use.

Patient and Treatment Assessment

Before each hemodialysis treatment, the patients completed a questionnaire rating the previous treatment as worse than average, average, or better than average. They were also asked to assess the 12 h after the previous treatment for the presence or absence of the following symptoms: muscle cramps, dizziness, malaise, thirst, and pruritus.

At each dialysis treatment, the interdialytic weight gain, the pretreatment and posttreatment weights, the blood pressure, and the heart rate were recorded. Postdialysis blood pressures were measured with the patient in the seated position immediately after the completion of the treatment. The presence or absence of the following intradialytic symptoms and signs was noted: nausea, vomiting, headache, pruritus, and symptomatic hypotension. Symptomatic hypotension was defined as a decrease in blood pressure temporally associated with symptoms. Cramps were quantitated as none, mild, or severe, i.e., lasting for longer than 5 min. The amount of saline administered, the number of times the ultrafiltration rate was decreased, and any other interventions were
and hematocrits were measured by freezing point depression (Precision Systems, Inc., Sudbury, MA) and capillary tube centrifugation, respectively.

**Statistical Analysis**

The continuous variables were normally distributed, and one-way analysis of variance, controlling for the multiple observations contributed by each patient, was used. The overall effect of sodium modeling was determined by F test, and when a significant effect was found, paired differences were examined with Duncan's multiple range test.

The percentages of constant, exponential, linear, and step treatments during which symptoms occurred were calculated. Each sign or symptom was viewed as binary. Because the percentages did not control for individual patient variation, logistic regression analysis was used to control for the possibility that symptoms occurred frequently in a small number of patients. The odds ratios for signs and symptoms not occurring during the modeled programs as compared with the constant (reference) program were calculated. The treatments on modeled programs were analyzed both as individual programs and as a group. Odds ratios were constructed such that values greater than 1.0 indicate that a sign or symptom was less likely to occur on a particular program than during the treatments with constant sodium dialysate. Differences among the programs were tested with the likelihood-ratio χ² test. In addition, relationships between signs and symptoms and continuous physiologic measures, irrespective of sodium program, were examined with logistic regression. The multiple observations contributed by each patient were controlled for in all of the analyses.

**RESULTS**

Sixteen patients completed the study. In general, adverse events occurred more frequently during treatments with a constant dialysate sodium than during treatments with sodium modeling (Table 1). The frequency of intradialytic headache and nausea and interdialytic fatigue and dizziness was markedly decreased with sodium modeling.

Table 2 lists the odds of improvement for symptoms during the exponential, linear, and step programs and for all modeling combined. When all sodium programs were grouped and compared with constant dialysate sodium, significant improvement was observed in 7 of 13 signs and symptoms. For example, intradialytic muscle cramps were 1.8 times less likely to occur during a modeled treatment than during the constant treatment protocol. Modeling also provided significant improvement in intradialytic headache and nausea; posttreatment hypotension; and interdialytic fatigue, dizziness, and muscle.
cramping (all \( P < 0.05 \)). Patients were more than three times less likely to rate modeled treatments as average or below average (as opposed to above average) compared with treatments on constant dialysate sodium (\( P < 0.05 \)).

Significant differences were also seen among individual programs. The linear and step programs, for example, were significantly better in lowering the risk of intradialytic headache than was the exponential program (\( P < 0.05 \)). The linear program was the only individual program that alleviated intradialytic cramps (\( P < 0.05 \)). Most striking was the decrease in the risk of posttreatment hypotension with the step program. Patients on the step program were 10.6 times less likely to experience hypotension at the conclusion of their treatments than after dialysis with the constant dialysate sodium protocol (\( P < 0.05 \)). Hypotension also occurred less frequently after the step program than after the linear and exponential programs (\( P < 0.05 \)). The decrease in postdialysis hypotension after the step program occurred despite the ultrafiltration of a greater percentage of the dry weight during the step program (4.7%) than during the constant protocol (3.8%), the linear (4.2%) program, or the exponential (4.1%) program (\( P < 0.05 \)).

There was no difference in the incidence of symptomatic hypotension during hemodialysis among the treatment regimens. The individual programs did not vary in the likelihood of posttreatment tachycardia, intradialytic thirst, pretreatment hypertension, or the degree of intradialytic weight gain (mean, 4.3% of dry weight). Similarly, there were no differences in the predialysis and postdialysis serum sodium concentrations, the degree of intradialytic hemoconcentration (mean, 16.5%), or the magnitude of the decrease in serum osmolality (mean, 22 mosm/kg).

Several significant associations between physiologic changes and dialytic symptoms were noted when all treatment regimens were combined (Table 3). First, the rate of ultrafiltration (percentage of dry weight ultrafiltered per hour) was associated with intradialytic cramps, nausea, and symptomatic hypotension, but not with headache. In contrast, the degree of hemoconcentration was related only to intradialytic cramps. The change in hematocrit was also associated with the volume of fluid ultrafiltered (data not shown; \( P < 0.001 \)). The change in osmolality was associated with headache (\( P = 0.07 \)) and nausea (\( P = 0.08 \)), but not with cramps or hypotension. Finally, the intradialytic weight gain was highly associated with intradialytic cramps, headache, nausea, and episodes of symptomatic hypotension. The larger the weight gain, the more likely a patient was to have these symptoms.

**DISCUSSION**

This study clearly demonstrates that the use of sodium modeling is associated with decreased dialytic morbidity in young hemodialysis patients. Sodium modeling significantly ameliorated intradialytic nausea, headache, and cramping; posthemodialysis hypotension; and intradialytic fatigue, dizziness, and cramping. The only comparable study of sodium modeling assessed older patients receiving high-flux dialysis (19). Acchiardo and Hayden found a 50% reduction in the incidence of hypotension and cramping and a marked decrease in the amount of normal saline required when sodium modeling was used. Dialysis disequilibrium symptoms, such as headache and nausea, were not assessed.
TABLE 2. Odds ratios for improvement of signs and symptoms during sodium modeling as compared with constant treatment

<table>
<thead>
<tr>
<th>Intradialytic Signs and Symptoms</th>
<th>Exponential&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Linear</th>
<th>Step</th>
<th>All Modeling&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cramps during HD&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.7 (0.8, 3.5)</td>
<td>1.8 (0.9, 3.8)</td>
<td>1.9 (0.9, 3.9)</td>
<td>1.8 (1.0, 3.3)</td>
</tr>
<tr>
<td>Headache during HD</td>
<td>1.0 (0.4, 2.3)</td>
<td>3.1&lt;sup&gt;c&lt;/sup&gt; (1.2, 8.0)</td>
<td>4.2&lt;sup&gt;c&lt;/sup&gt; (1.5, 11.8)</td>
<td>2.1&lt;sup&gt;d&lt;/sup&gt; (1.0, 4.3)</td>
</tr>
<tr>
<td>Nausea during HD</td>
<td>4.8&lt;sup&gt;d&lt;/sup&gt; (1.8, 12.8)</td>
<td>3.6&lt;sup&gt;d&lt;/sup&gt; (1.4, 8.9)</td>
<td>3.5&lt;sup&gt;d&lt;/sup&gt; (1.4, 8.6)</td>
<td>3.9&lt;sup&gt;d&lt;/sup&gt; (1.9, 7.8)</td>
</tr>
<tr>
<td>Pruritus during HD</td>
<td>1.8 (0.8, 3.9)</td>
<td>1.0 (0.5, 2.3)</td>
<td>0.9 (0.4, 2.0)</td>
<td>1.2 (0.5, 2.3)</td>
</tr>
<tr>
<td>Symptomatic hypotension during HD</td>
<td>1.0 (0.5, 2.1)</td>
<td>1.0 (0.5, 2.0)</td>
<td>1.9 (0.9, 4.1)</td>
<td>1.2 (0.7, 2.2)</td>
</tr>
<tr>
<td>Any boluses of NaCl during HD</td>
<td>1.2 (0.6, 2.2)</td>
<td>1.5 (0.8, 2.9)</td>
<td>1.8 (0.9, 3.4)</td>
<td>1.5 (0.9, 2.5)</td>
</tr>
<tr>
<td>Post-HD hypotension</td>
<td>1.6 (0.5, 5.0)</td>
<td>2.3 (0.7, 7.5)</td>
<td>10.6&lt;sup&gt;c&lt;/sup&gt; (2.5, 45.9)</td>
<td>2.9&lt;sup&gt;d&lt;/sup&gt; (1.1, 7.4)</td>
</tr>
<tr>
<td>Post-HD tachycardia</td>
<td>1.9 (0.5, 7.0)</td>
<td>0.8 (0.2, 2.8)</td>
<td>0.7 (0.2, 2.3)</td>
<td>1.0 (0.4, 2.7)</td>
</tr>
<tr>
<td>Interdialytic Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue between HD</td>
<td>3.4&lt;sup&gt;d&lt;/sup&gt; (1.5, 6.3)</td>
<td>3.4&lt;sup&gt;d&lt;/sup&gt; (1.7, 6.8)</td>
<td>4.4&lt;sup&gt;d&lt;/sup&gt; (2.1, 9.1)</td>
<td>3.6&lt;sup&gt;d&lt;/sup&gt; (2.0, 6.4)</td>
</tr>
<tr>
<td>Thirst between HD</td>
<td>1.1 (0.5, 2.5)</td>
<td>1.0 (0.4, 2.2)</td>
<td>0.6 (0.3, 1.4)</td>
<td>0.9 (0.5, 1.7)</td>
</tr>
<tr>
<td>Dizziness between HD</td>
<td>2.4&lt;sup&gt;d&lt;/sup&gt; (1.2, 4.8)</td>
<td>2.4&lt;sup&gt;d&lt;/sup&gt; (1.2, 4.8)</td>
<td>5.2&lt;sup&gt;d&lt;/sup&gt; (2.4, 11.2)</td>
<td>3.0&lt;sup&gt;d&lt;/sup&gt; (1.7, 5.2)</td>
</tr>
<tr>
<td>Cramps between HD</td>
<td>1.6 (0.7, 3.6)</td>
<td>2.3&lt;sup&gt;d&lt;/sup&gt; (1.0, 5.2)</td>
<td>2.0 (0.9, 4.5)</td>
<td>1.9&lt;sup&gt;d&lt;/sup&gt; (1.0, 3.8)</td>
</tr>
<tr>
<td>Pruritus between HD</td>
<td>1.7 (0.7, 4.3)</td>
<td>0.4&lt;sup&gt;a&lt;/sup&gt; (0.2, 0.8)</td>
<td>0.7 (0.3, 0.8)</td>
<td>0.7 (0.4, 1.5)</td>
</tr>
<tr>
<td>Patient Perception of Treatment</td>
<td>3.4&lt;sup&gt;d&lt;/sup&gt; (1.5, 7.6)</td>
<td>3.4&lt;sup&gt;d&lt;/sup&gt; (1.5, 7.5)</td>
<td>3.9&lt;sup&gt;d&lt;/sup&gt; (1.7, 8.9)</td>
<td>3.6&lt;sup&gt;d&lt;/sup&gt; (1.9, 6.7)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Odds ratio (95% confidence interval).
<sup>b</sup> All modeling, treatments with exponential, linear, and step programs combined.
<sup>c</sup> HD, hemodialysis treatment(s).
<sup>d</sup> Significantly different from constant (P < 0.05).
<sup>e</sup> Significantly different from exponential (P < 0.05).
<sup>f</sup> Significantly different from linear (P < 0.05).

TABLE 3. Associations between physiologic changes and adverse effects<sup>g</sup>

<table>
<thead>
<tr>
<th></th>
<th>Change in Hematocrit</th>
<th>Change in Osmolality</th>
<th>Interdialytic Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cramps During HD</td>
<td>P &lt; 0.0001</td>
<td>NS</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Headache during HD</td>
<td>NS</td>
<td>P = 0.07</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Nausea During HD</td>
<td>NS</td>
<td>P = 0.08</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Symptomatic Hypotension During HD</td>
<td>NS</td>
<td>NS</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

<sup>g</sup> All treatments, both constant and modeled, are combined. HD, hemodialysis treatment; NS, not significant.

Previous studies using a constantly high-sodium dialysate have also shown improvement in intradialytic symptoms (14–17). Some of these studies, however, did not find any improvement in cramps, headache, or nausea. In addition, some patients have had significant increases in interdialytic weight gain (15,17) or exacerbation of hypertension (16). Although infrequent, pulmonary edema has also been reported with the use of a high-sodium dialysate (21). All of the constantly high-sodium studies, however, were performed in older patients dialyzed with dialysate containing acetate, a probable vasodilator (22). These variables prevent the strict comparison of this study with the high-sodium studies. We found none
of the adverse effects that have been previously reported with high-sodium dialysate. Specifically, no increase in interdialytic thirst, interdialytic weight gain, pretreatment hypertension, or the development of pulmonary edema was seen. The fact that there was no increase in the posttreatment serum sodium concentration in this study most likely accounted for the lack of adverse effects. The lack of adverse effects should be viewed as a major advantage of sodium modeling over the use of constantly high-sodium concentrations in the dialysate. In a future study, it might be of interest to compare these sodium programs with a higher constant dialysate sodium concentration.

A unique finding of this study is the demonstration that particular sodium programs selectively improved individual symptoms. Previous reports have only shown differences between constant dialysate sodium treatments and modeling when all of the various modeling programs were statistically combined (19). In this study, the linear and step programs were significantly better than both the constant and exponential protocols in preventing headaches, whereas the linear program was the only program that significantly decreased interdialytic cramps. The most striking improvement was the decrease in postdialysis hypotension seen with the step program. Despite the greater ultrafiltration rate during step treatments, there was no increase in intradialytic adverse effects. As a consequence of the prolonged increase in dialysate sodium, fluid movement from the interstitial space into the intravascular compartment may have been more sustained. In addition, the rate of fluid mobilization into the intravascular compartment may have been more rapid (23). As a result, plasma volume was most likely better preserved during the step program. Plasma volume, not extracellular fluid volume, interstitial fluid volume, or the change in urea concentration, has been suggested to be the primary determinant of systolic blood pressure during dialysis (5).

In contrast to the results of this study, Acchiardo and Hayden (19) observed a greater improvement in intradialytic hypotension with sodium modeling. Those investigators, however, were unable to demonstrate that specific symptoms were preferentially relieved with the use of particular programs. The differences between the findings of Acchiardo and Hayden and those of this study may be attributable to differences in the baseline incidence of hypotension, the type of dialysis (high flux versus conventional), and/or the ages of the patients evaluated. The study population presented here, with a median age of 19, may have different vascular and hemodynamic characteristics than an older population. This study population was likely more homogeneous, with less baseline hemodynamic instability, than an older population. Further, patients receiving long-term hemodialysis may develop some degree of autonomic insufficiency (24,25). Therefore, vascular reactivity may differ significantly between younger and older hemodialysis patients. In addition, none of the patients in this study had diabetes mellitus or chronic hypertension. The relative contribution of patient age, number of years on hemodialysis, or coexisting diseases to dialytic symptoms is not clear. However, the effects of sodium modeling may be more evident in young hemodialysis patients without the alterations produced by long-term disease.

Although this study was not designed to examine the physiologic bases for dialytic morbidity, the associations that emerged provide some insight into these phenomena. Hypotension occurred more frequently with larger interdialytic weight gains that necessitated greater ultrafiltration rates. This finding is consistent with the observation that, at low ultrafiltration rates, plasma refilling can almost completely compensate for the decrease in plasma volume. At higher ultrafiltration rates, however, the gap between the ultrafiltration rate and the refilling rate increases; refilling cannot then compensate for ultrafiltration (26). There was also a borderline association between the decrease in serum osmolality during dialysis and the occurrence of headaches and nausea. This finding is consistent with a role for brain cell swelling or dysfunction in the development of these symptoms.

Sodium modeling markedly decreased intradialytic and interdialytic morbidity in young hemodialysis patients. Unique to this study is the finding that particular sodium modeling programs selectively alleviated individual symptoms. Therefore, the optimal sodium program for an individual patient may vary with that patient's dialysis symptoms. The observed benefits of sodium modeling and the lack of adverse effects strongly support more widespread trials and applications of its use.

ACKNOWLEDGMENTS

We thank the family of Christine M. Goodwin for their generous support of this study. R.H. Sadowski was supported in part by grant T32HD-07268 from the NIH. We thank Terry Law, B.S., M.T., S.C. (ASCP), Clinical Chemistry Supervisor, for his technical assistance. We acknowledge the nurses of the Renal Dialysis Unit at Children's Hospital for their assistance with data collection. In particular, we thank Cathy Macirowski, B.S.N., R.N., Linda Gorynski, A.D., R.N., Danielle Boyer, A.D., R.N., and Floreen Knight, B.S.N., R.N., for their assistance with the development of the study protocol and data collection. We thank William E. Harmon, M.D. for critical reading of the manuscript.

REFERENCES

17. Barre PE, Brunelle G, Gascon-Barre M: A randomized double blind trial of dialysate sodiums of 145 mEq/L, 150 mEq/L, and 155 mEq/L. ASA1O Trans 1988;34:338-341.

Sodium Modeling in Hemodialysis Patients