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Long-Term Stability of Serum Sodium in Hemodialysis Patients

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Key Words
Serum sodium · Hemodialysis · Dialysate sodium

Abstract
Background: A direct relationship between dialysate-to-plasma sodium gradient, blood pressure and interdialytic weight gain exists in hemodialysis (HD) patients. The aim of this study was to delineate the long-term variability of serum sodium in HD patients. ***Methods:*** We performed a retrospective cohort analysis of serum sodium and other analytes routinely evaluated in 100 stable chronic HD patients observed for 12 months. ***Results:*** Individual levels across the cohort varied from 122 to 145 mM, but 12-month intraindividual coefficients of variation for sodium were low (pre-HD = 1.6%; post-HD = 1.8%) with overall variability similar to that related to laboratory assay variability especially when compared with other analytes (3.1–30.8%). Pre-HD serum sodium had a trend toward hyponatremia (mean 136 ± 0.8 mM). ***Conclusion:*** Serum sodium is stable over time in HD patients. Pre-HD serum sodium may be used as a parameter for individualizing dialysate sodium prescription.

Introduction

Sodium and water balance is the most important factor in determining blood pressure in dialysis patients. Our group demonstrated that individualizing dialysate sodium prescription reduces thirst, interdialytic weight gain and blood pressure in hypertensive patients [1]. In that short-term study, sodium prescription was based on data suggesting that pre-hemodialysis (pre-HD) serum sodium varies little over time, with each patient having his/her osmolar set point [2]. Corroborating these findings, we observed that despite a mean reduction of approximately 3 mM in the prescribed dialysate sodium, pre-HD serum sodium did not change [1]. Because previous studies were either of short duration or included too few patients, we decided to analyze serum sodium variability in a larger cohort over a longer period of time, and to compare it with the variability of other commonly obtained laboratory tests.

Methods

We performed a retrospective cohort analysis of 100 chronic HD patients at the VA Connecticut Healthcare System (West Haven, Conn., USA) observed for 3–12 months (median 12 months). The local Institutional Review Board approved the project and granted a waiver of informed consent.

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Table 1. Twelve-month variability of serum chemistries in 100 stable hemodialysis patients

Biochemical parameter	Timing	Twelve-month average ± SD	Twelve-month intraindividual coefficient of variation	Laboratory coefficient of variation for the assay
Sodium, mM	Pre-HD	136.4 ± 0.8	1.6%	0.6%
	Post-HD	137.8 ± 0.9	1.8%	
Potassium, mM	Pre-HD	5.1 ± 0.6	11.6%	1.8%
	Post-HD	3.8 ± 0.4	10.1%	
Chloride, mM	Pre-HD	100.5 ± 4.1	4.0%	0.8%
	Post-HD	100.2 ± 3.1	3.1%	
Bicarbonate, mM	Pre-HD	22.1 ± 2.6	11.8%	5.7%
	Post-HD	25.1 ± 2.6	10.3%	
Calcium, mg/dl	Pre-HD	9.0 ± 0.6	24.1%	1.7%
Phosphorus, mg/dl	Pre-HD	5.4 ± 1.3	25.1%	2.2%
Blood urea nitrogen, mg/dl	Pre-HD	58.8 ± 13.2	23.0%	3.4%
	Post-HD	19.4 ± 5.9	30.8%	
Creatinine, mg/dl	Pre-HD	9.6 ± 2.1	18.4%	5.7%
	Post-HD	3.9 ± 0.9	20.9%	
Glucose, mg/dl	Pre-HD	134.0 ± 35.5	24.1%	1.4%
	Post-HD	127.8 ± 23.9	17.8%	
Albumin, g/dl	Pre-HD	3.8 ± 0.4	8.8%	1.6%

Intraindividual coefficient of variation was calculated as the standard deviation of the intraindividual means over 12 months divided by the intraindividual means during the same period.

Laboratory coefficients of variation were obtained from the VA Connecticut Central Laboratory. They represent laboratory control measures for assay performance and include both within-day and between-day variability within a single lot. These coefficients are not specific to dialysis patients.

Patients were dialyzed with conventional bicarbonate HD on standard HD machines (Cobe Centrysystem 3 and Fresenius 2008K) using modified cellulose, polymethylmethacrylate or polysulfone membranes. The base dialysate sodium concentration used was 140 mM, though some patients underwent sodium profiling. Potassium, bicarbonate and calcium concentrations were prescribed by the treating clinician according to individual needs. We did not collect data on interdialytic weight gain and ultrafiltration.

Pre- and post-HD serum sodium were obtained from patients' records. Because hyperglycemia can decrease serum sodium concentration by shifting water from intracellular compartment, we adjusted serum sodium levels to the paired serum glucose level (1.6 mM per 100 mg/dl above 200 mg/dl) in diabetic patients [3]. In addition, we collected data on variables that are potentially relevant to water and thirst homeostasis, such as the use of blockers of the renin-angiotensin system, psychiatric diagnoses, antipsychotic/antidepressant drug use, and geographic area of residence (to account for differences in temperature and humidity).

We also collected data on pre- and post-HD serum levels of blood urea nitrogen, chloride, potassium, bicarbonate, creatinine and glucose, and pre-HD serum levels of calcium, phosphorus and albumin. Serum analytes were processed through the Abbott Architect module (Abbott Laboratories, Abbott Park, Ill., USA). Serum sodium was measured by indirect ionometry (ion-specific electrode using diluted specimens).

Statistical Analysis

Results are depicted as means ± SD for all variables. Variability over time was established by determination of the coefficient of variation (standard deviation/mean × 100) for each laboratory test.

Results

All patients were men, aged 64 ± 11 years. All patients had three HD sessions a week. With respect to other variables of relevance to osmoregulation and interpretation of serum sodium values, 47% were diabetic, 13% were on antidepressants, 6% had a diagnosis of schizophrenia (4 on antipsychotic medications), 50% received a blocker of the renin-angiotensin system, and all resided in the same geographic area (Connecticut, USA).

Individual levels across the cohort varied from 122 to 145 mM. The mean 12-month glucose-adjusted pre-HD serum sodium was 136 ± 0.8 mM (range: 128.0–140.2 mM) with a low coefficient of variation (1.6%) that was very similar to that related to laboratory assay variability

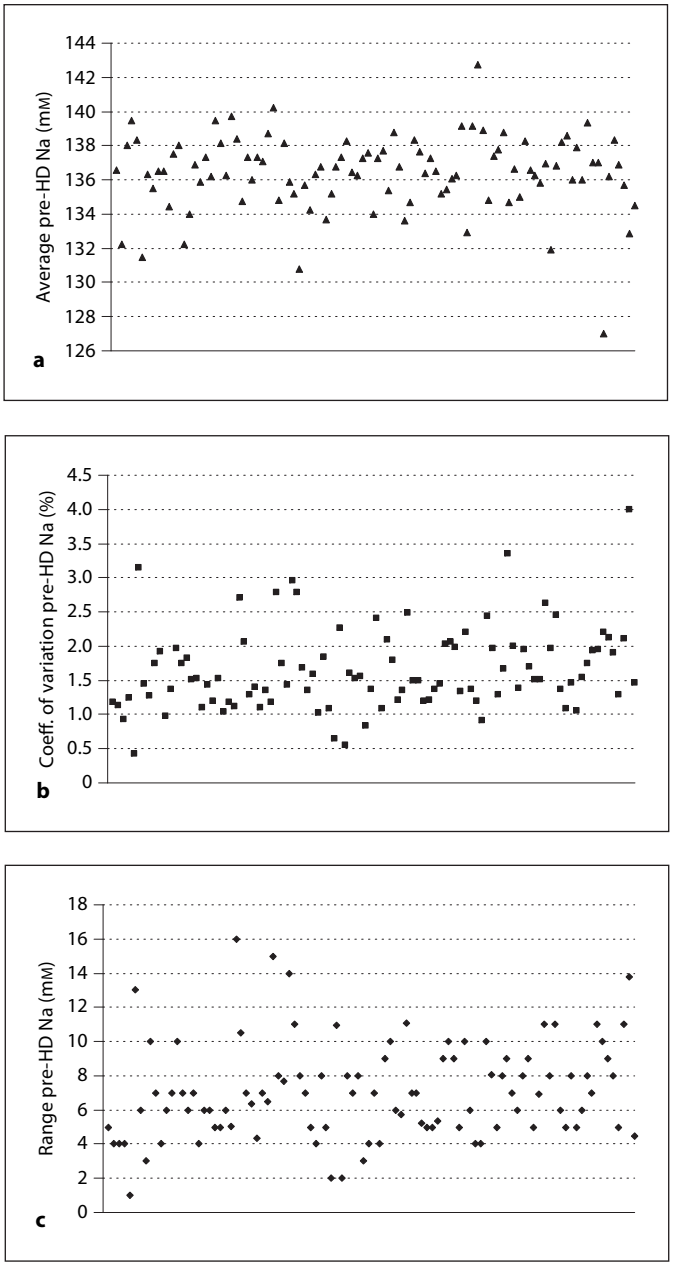

Fig. 1. Individual pre-dialysis serum sodium average (**a**), pre-dialysis serum sodium coefficient of variation (**b**), and range of pre-dialysis serum sodium (**c**). Each symbol represents an individual patient.

(table 1). This behavior was consistent across strata of average sodium levels: the pre-HD coefficient of variation was 2.2% for patients with average sodium <135 mM (n = 20), 1.6% for those between 135 and 137.9 mM (n = 60), and 1.3% for those averaging ≥138 mM (n = 20).

Despite the low coefficient of variation, the average range of observed serum sodium was relatively high (7.1 mM), and 21 subjects had a range ≥10 mM. In other words, serum sodium was reproducible on most months of the year, but outlier readings occurred on occasion, often resulting in a high range. Figure 1 depicts the individual averages, variability and ranges of pre-HD serum sodium in each study participant.

Only 5 patients had mean pre-HD serum sodium levels ≥140 mM. Post-HD serum sodium coefficient of variation was also low (1.8%) despite the fact that post-HD serum sodium was significantly higher than pre-HD serum sodium (138 ± 0.9 mM; $p < 0.0001$ vs. pre-HD). There were no differences according to diabetic status, degree of glycemic control, use of a blocker of the renin-angiotensin system, or coexistence of a psychiatric diagnosis or treatment. There was a significant correlation between the size of the dialysate-to-plasma sodium gradient and the pre-HD sodium CV ($r = 0.45$, $p < 0.001$). However, the clinical relevance of this correlation was minimal: patients with a gradient below the median (3.4 mM) had a pre-HD sodium CV of 1.4%, whereas those with a gradient above the median had a pre-HD sodium CV of 1.8% ($p < 0.001$). In sharp contrast to sodium, other analytes exhibited coefficients of variation that were higher than the laboratory assay variability (table 1).

Discussion

Our study corroborates that serum sodium has long-term stability in HD patients and that there is a trend toward hyponatremia. It implies that a standard dialysate sodium prescription greater than 138 mM results in a positive dialysate-to-plasma sodium gradient in the majority (80%) of patients [4, 5]. Indeed, our patients had a significant increase in post-HD serum sodium, likely related to the standard dialysate sodium prescription of 140 mM. While it is convection that is responsible for most of intradialytic sodium losses, diffusive losses based on the dialysate-to-plasma gradient are important in the 'fine tuning' of sodium balance in HD patients.

We noted limited variability of serum sodium levels throughout the year, which is in contrast to recent observations in 44 Chinese peritoneal dialysis patients (5%) [6], but in agreement with previous data evaluating seasonal variability of biochemical parameters in 1,172 HD patients in the US (0.6%, which was statistically significant but of minimal clinical relevance) [7], possibly implicating dialysis modality and/or differences in climate as re-

sponsible factors. On the other hand, predialysis sodium levels may be occasionally 'off', as indicated by the average range of 7.1 mM (as high as 16 mM in one of our subjects), demonstrating that a single measurement may not reflect the average pre-HD serum sodium.

The long-term consistency of individual serum sodium levels suggests that HD patients maintain an osmolar set point despite the loss of kidney and vasopressin feedback mechanisms that have a fundamental role in osmoregulation [8]. Therefore, it is thirst that is the main mechanism controlling extracellular osmolality in patients on chronic maintenance HD. Because thirst is influenced by salt intake and serum sodium levels, and dialysate sodium is a key modulator of both of these factors, attention to dialysate sodium concentration is an important component of the chronic HD prescription. A positive dialysate-to-plasma sodium gradient may result in increased thirst, interdialytic weight gain and blood pressure [4, 5, 9]. The detrimental results of such relationship has been suggested by data from a cohort of 4,649 HD patients [10], wherein interdialytic weight gain followed the dialysate-to-plasma sodium gradient, and a gradient in excess of 3 mM was associated with increased mortality.

In addition to the fact that eliminating a positive dialysate-to-plasma sodium gradient reduces thirst, interdialytic weight gain and blood pressure [1], the possibility that dialysate sodium concentration may influence the 'osmolar set point' of HD patients should be considered. It is possible that forcing a negative sodium balance through a negative dialysate-to-plasma sodium gradient causes a change in the patient's osmoregulation. For example, a longer-term (4 months) random reduction of 3 mM in dialysate sodium prescription (141–138 mM) was associated with a significant decrease in pre-HD serum sodium [11]. The detrimental effects of sodium in chronic kidney disease have been emphasized [12] and support actions to try to reduce sodium burden such as prescribing a dialysate with sodium concentration below the patient's prevailing plasma sodium concentration. However, the limits of safety for this practice must still be established.

The major limitation of our study is the absence of other relevant data such as interdialytic weight gain and blood pressure levels. Although we acknowledge the importance of these data in describing an HD population and the fact that their knowledge might have given us further insights into our findings, we believe that they would not have an impact on our key observation that serum sodium levels are stable in HD patients.

In conclusion, our study confirms that serum sodium has limited variability over time. Pre-HD serum sodium can be used to guide dialysate sodium prescription, although it remains to be confirmed that long-term dialysate sodium reduction may alter the individual osmolar set point without side effects.

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