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BODY SODIUM, POTASSIUM AND WATER IN PERITONEAL DIALYSIS-ASSOCIATED HYPONATREMIA

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♦ ***Objective:*** **This report presents a method quantitatively analyzing abnormalities of body water and monovalent cations (sodium plus potassium) in patients on peritoneal dialysis (PD) with true hyponatremia.**

♦ ***Methods:*** **It is well known that in the face of euglycemia serum sodium concentration is determined by the ratio between the sum of total body sodium plus total body potassium on the one hand and total body water on the other. We developed balance equations that enabled us to calculate excesses or deficits, relative to the state of eunatremia and dry weight, in terms of volumes of water and volumes of isotonic solutions of sodium plus potassium when patients presented with hyponatremia. We applied this method retrospectively to 5 episodes of PD-associated hyponatremia (serum sodium concentration 121–130 mEq/L) and compared the findings of the method with those of the clinical evaluation of these episodes.**

♦ ***Results:*** **Estimates of the new method and findings of the clinical evaluation were in agreement in 4 of the 5 episodes, representing euvolemic hyponatremia (normal total body sodium plus potassium along with water excess) in 1 patient, hypovolemic hyponatremia (deficit of total body sodium plus potassium along with deficit of total body water) in 2 patients, and hypervolemic hyponatremia (excess of total body sodium along with larger excess of total body water) in 1 patient. In the 5th patient, in whom the new method suggested the presence of water excess and a relatively small deficit of monovalent cations, the clinical evaluation had failed to detect the cation deficit.**

♦ ***Conclusions:*** **Evaluation of imbalances in body water and monovalent cations in PD-associated hyponatremia by the method presented in this report agrees with the clinical evaluation in most instances and could be used as a guide to the treatment of hyponatremia. Prospective studies are needed to test the potential clinical applications of this method.**

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KEY WORDS: Hyponatremia; euvolemia; hypovolemia; hypervolemia; water balance; sodium balance; potassium balance.

True (hypotonic) hyponatremia is associated with high levels of morbidity and mortality in the general population (1), in addition to the high costs of medical care (2). True hyponatremia is also associated with an increased risk of death in patients on chronic hemodialysis (3). In the general population, 3 general categories of true hyponatremia are recognized: hypervolemic, hypovolemic, and euvolemic (1,4–6). Assigning a patient to the proper category is important because of substantial differences in the management of hyponatremic states (1,5,6).

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Although infrequent, hyponatremia is encountered in peritoneal dialysis (PD) patients (7). Identifying the diagnostic category (hypervolemic, hypovolemic, or euvolemic) of hyponatremia would serve to guide the therapeutic measures in hyponatremia developing in PD patients as it would with hyponatremia in the general population. Hypervolemia with excessive body sodium is a recognized cause of PD-associated hyponatremia, but low total body sodium has also been found in some instances (8–10). We present a quantitative evaluation of imbalances in body water and electrolytes in true hyponatremia developing in PD patients. This evaluation leads to the classification of an episode of PD-associated hyponatremia as hypervolemic, hypovolemic, or euvolemic. Data from episodes of hyponatremia in 5 patients maintained on PD were used to illustrate this method.

METHODS

QUANTITATIVE ANALYSIS OF MONOVALENT CATION AND WATER BALANCES IN HYPONATREMIA

Quantitative analyses of hyponatremia (4,11) are based on the fundamental observation of Edelman *et al.* that when serum glucose concentration ($[Glu]_s$) is not high, the only determinants of serum sodium concentration ($[Na]_s$) are total body water, total body sodium and total body potassium (12). Potassium is included because it is, by and large, the main intracellular cation. The ratio of total body monovalent cations, that is of the sum of total extracellular cation (sodium) plus total intracellular cation (potassium) over total body water is the biological variable that determines $[Na]_s$ in euglycemia (12,13). In patients with significant potassium deficits, hyponatremia is not corrected without appropriate potassium repletion (14). Not accounting for the amount of potassium replaced during treatment of hyponatremia can lead to a rapid rise in $[Na]_s$ with dire neurological consequences (15).

Based on Edelman's findings, Nguyen and Kurtz (16) developed a formula for determining the concentration of sodium in plasma water of patients treated with PD. A simplified form of Edelman's formula, proposed by Rose (17) is shown in the Appendix (formula 1). The superiority of the method proposed by Nguyen and Kuntz over methods based on the Rose's equation has not been shown in praxis. A study in critically ill patients who were not on dialysis (18) compared the estimates of urinary losses of water and monovalent cations calculated by another Nguyen-Kurtz method (19) based on the principles of Edelman's formula on the one hand and those estimates based on Rose's formula on the other. No significant differences between the 2 methods were found. The relation between changes in $[Na]_s$ and estimates of urinary losses calculated by the 2 methods also did not differ (18). Our method was based on Rose's formula, which is simpler.

The analysis presented in this report addresses the changes in the balances of water and monovalent cations (sodium plus potassium) accompanying true (hypotonic) hyponatremia developing in PD patients. Hypertonic hyponatremia and pseudo-hyponatremia (5) were not analyzed. The method consists of deriving equations characterizing the state of eunatremia and normovolemia and then using these equations and the changes in body weight and in $[Na]_s$ to derive formulas estimating excesses or deficits of total monovalent cations and water that have led to the hyponatremia. To allow calculation of the water that is required to be removed to normalize $[Na]_s$ in hyponatremic patients on PD after the cation balance is restored, these excesses or deficits are expressed as volumes of isotonic monovalent cation solution and volumes of water.

The analysis proceeds in 3 stages. Stage A represents a stage of eunatremia at dry weight. At this stage, body water is computed by anthropometric formulas utilized in the PD literature (20). In addition, 3 estimates of total body sodium plus potassium content are computed for patients who are in stage A. The higher limit (at a $[Na]$s value of 143 mEq/L), the lower limit (at a $[Na]_s$ value of 137 mEq/L), and the average value (at a $[Na]_s$ value of 140 mEq/L) of the normal range of $[Na]_s$ are used to calculate these 3 estimates.

Stage B represents a stage of hyponatremia. In this stage, body weight differs, more often than not, from dry weight. Body water is calculated as the body water estimate obtained during the dry weight period plus the change in body weight observed between the hyponatremia period and the dry weight period. This calculation assumes that the weight change between the 2 periods represents exclusively a change in body water. Estimates of the sum of body sodium plus body potassium in stage B are then computed.

Stage C is a comparison of the estimates of body water and total body sodium plus potassium between stages B and C. This comparison leads to the classification of hyponatremia as euvolemic, hypervolemic or hypovolemic. The classification is based on the comparisons of the estimates of total body sodium plus potassium, not the comparison of the estimates of total body water. Hyponatremia with normal sum of body sodium plus potassium is classified as euvolemic. By definition, euvolemic hyponatremia is characterized by an excess of

body water. Hyponatremia with total body monovalent cation deficit is classified as hypovolemic. In hypovolemic hyponatremia, body water may be below, at, or above the dry weight value. Hyponatremia with excessive body sodium (detectable total body potassium excesses are most probably incompatible with life) is classified as hypervolemic. Hypervolemic hyponatremia results schematically from gain of both a volume of isotonic saline plus an additional volume of body water. Figure 1 presents the method presented in this report. An Appendix, appearing as supplemental online material, contains details and the equations of the method.

ILLUSTRATIVE PATIENTS

The method presented was applied in the quantitative analysis of episodes of true hyponatremia ($[Na]_S \leq 130$ mEq/L, euglycemia) which developed during the course of PD in 5 patients. The episodes analyzed illustrate various categories of hyponatremia. Estimates of the volume of isotonic solutions containing monovalent cations that needed to be infused or removed plus the volume of water that needed to be removed to return the subjects to dry weight and eunatremia were calculated by applying the balance formulas derived in the Appendix to these hyponatremic episodes. These episodes preceded the development of the method presented in this report. Consequently, this method was not used to manage the episodes of hyponatremia described. Instead, the findings of this method were compared to the clinical evaluation and management of the hyponatremic episodes.

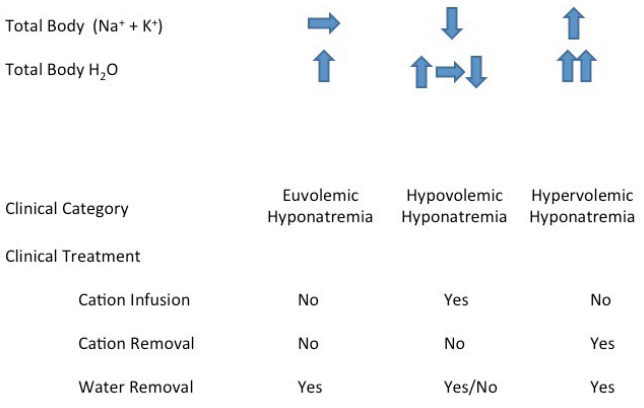

Figure 1 — Classification and management of true hyponatremia in PD patients.

RESULTS

Table 1 shows clinical characteristics of the 5 patients and the $[Na]_S$, serum potassium concentration ($[K]_S$) and $[Glu]_S$ at the time of hyponatremia. Renal failure was caused by diabetic nephropathy in 2 patients, glomerulonephritis in 2, and systemic lupus erythematosus in 1 patient. One patient was female and the other 4 were male. At the hyponatremic episode, the age of the patients varied between 23 and 68 years and the duration of PD varied between 1 and 72 months. Patients 3 and 4 were on continuous ambulatory peritoneal dialysis with 4 daily exchanges and 2-L fill volume. The remaining 3 patients were on combined nocturnal automated peritoneal dialysis and 1 or 2 daytime exchanges with daily fill volumes ranging between 10.5 and 15 liters. Patients 1, 2, 4 and 5 were anuric at the time of the hyponatremic episode.

Table 2 shows the values calculated by the method presented and the classification of the type of hyponatremia.

TABLE 1
Clinical Characteristics and Serum Values at the Time of Hyponatremia

Clinical characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Cause of renal failure	DM	SLE	GN	DM	GN
Gender	Male	Female	Male	Male	Male
Age, years	23	40	54	68	41
Height, cm	168	155	171	183	178
Dry weight, kg	65.0	61.4	71.2	91.0	85.7
Weight at hyponatremia, kg	71.8	52.3	76.3	95.3	83.0
PD duration, months	1	66	72	31	8
Clinical background	Post treatment of extreme hyperglycemia	Lethal calciphylaxis	Post severe peritonitis	Poor compliance	Nausea, vomiting, paresthesias
$[Na]_S$, mEq/L	121	128	130	124	129
$[K]_S$, mEq/L	3.7	4.3	3.5	3.4	6.5
$[Glu]_S$, mmol/L (mg/dL)	4.4 (80)	4.2 (76)	5.2 (94)	6.2 (112)	3.7 (67)

DM = diabetes mellitus; SLE = systemic lupus erythematosus; GN = glomerulonephritis; PD = peritoneal dialysis; $[Na]_S$ = serum sodium concentration; $[K]_S$ = serum potassium concentration; $[Glu]_S$ = serum glucose concentration.

TABLE 2
Classification of Hyponatremic Episodes

Calculated value	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
$H_2O_{Body,DW}$, L (Ref. 20)	40.20	29.60	39.66	46.21	46.49
$(Na_{Body} + K_{Body})_{DW}$, mEq, range (Formulas 3a, 3c)[a]	5,503–5,744	4,055–4,233	5,433–5,671	6,331–6,608	6,369–6,648
δH_2O_{Body}, L (Formula 4)[a]	6.8	-9.1	5.1	4.3	-2.7
$H_2O_{Body,\downarrow[Na]s}$, L (Formula 5)[a]	47.00	20.50	44.76	50.51	43.79
$(Na_{Body} + K_{Body})_{\downarrow[Na]s}$, mEq (Formula 6)[a]	5,687	2,624	5,819	6,263	5,649
$\delta H_2O_{Isotonic}$, L (Formulas 9, 11)[a]	Negligible	-10.86	1.90	-1.47	-6.14
$\delta(Na_{Body} + K_{Body})$, mEq (Formulas 10, 12)[a]	Negligible	-1520.4	266.0	-205.8	-859.6
δH_2O, *L* (Formula 7)[a]	6.8	1.76	3.20	5.77	3.44
Classification of hyponatremia	Euvolemic	Hypovolemic	Hypervolemic	Hypovolemic	Hypovolemic

$H_2O_{Body,DW}$ = body water at dry weight; $(Na_{Body} + K_{Body})_{DW}$ = body sodium plus potassium at dry weight; δH_2O_{Body} = body weight difference between the stages of hyponatremia and dry weight; $H_2O_{Body,\downarrow[Na]s}$ = body water at the stage of hyponatremia; $(Na_{Body} + K_{Body})_{\downarrow[Na]s}$ = body sodium plus potassium at the stage of hyponatremia; $\delta H_2O_{Isotonic}$ = excess or deficit of isotonic solution, with a sum of sodium plus potassium concentrations equal to 140 mEq/L, at the stage of hyponatremia; $\delta(Na_{Body} + K_{Body})$ = excess or deficit of monovalent cations at hyponatremia; δH_2O = water excess at the stage of hyponatremia.
[a] Appendix formula.

In patient 1, hyponatremia was classified as euvolemic. This patient had presented with extreme hyperglycemia after having omitted several PD sessions. He had finished the last PD session at his previously determined dry weight of 65.0 kg and had severe thirst and fluid consumption in the 2 days preceding his admission with hyperglycemia. At presentation, his $[Glu]_s$ was 68.9 mmol/L (1240 mg/dL), $[Na]_s$ was 103 mEq/L, and $[K]_s$ was 5.7 mEq/L. He was treated only with intravenous insulin. Serum values shown in Table 1 were obtained 16 hours after the onset of treatment. During those 16 hours he had no dialysis and had minimal oral intake. His weight was the same (71.8 kg) at presentation with hyperglycemia and after $[Glu]_s$ was normalized. The euglycemic $[Na]_s$ value of 121 mEq/L was used in the calculations because it is the value representing the Edelman and Rose formulas. These formulas exclude cases of hyperglycemia, in which extracellular gain of solute (glucose) leads to osmotic water exit from the intracellular into the extracellular compartment and dilution of extracellular sodium independently of any changes in external sodium, potassium or water balance. The classification of hyponatremia as euvolemic is consistent with his statement that he consumed only water after the end of his last PD session when he was at his dry weight. He resumed his regular PD schedule and hyponatremia was corrected in the next 3 days.

Patient 2 had symptomatic hypovolemia with hypotension and tachycardia. Infusion of 10.86 L of a solution with a sum of sodium plus potassium concentrations of 140 mEq/L would increase her body water from 20.5 L to 31.36 L, a value higher by 1.76 L than her dry weight body water value of 29.6 L. Thus, normalization of both body water and $[Na]_s$ in this patient would require removal of 1.76 L of water, in addition to the infusion of 10.86 L of isotonic solution with monovalent cation concentration of 140 mEq/L. The weight difference between the dry weight and the weight at the time of hyponatremia could have overestimated her water deficit, because she had developed a severe catabolic illness in the 3 months between the last determination of her dry weight and the hyponatremic episode. Nevertheless, both clinical evaluation and the use of the new method detected severe hypovolemia at the time of the hyponatremic episode. She received several liters of 0.154 m saline infusions with normalization of $[Na]_s$, but expired from sepsis within 1 week.

Analysis of the components of hyponatremia in patient 3, who had a weight gain of 5.1 kg, suggested that 1.9 L of this weight gain was due to retention of isotonic solution containing sodium at a concentration of 140 mEq/L, while 3.2 L of the weight gain was caused by water retention. Treatment with hypertonic dextrose dialysate in the next week resulted in correction of the hyponatremia and reduction of body weight.

Patient 4 had, at the time of hyponatremia, a 4.3-kg weight excess over his dry weight, but the analysis in Table 2 suggested the presence of hypovolemia with an

isotonic volume deficit of 1.47 L. Infusion of 1.47 L of a saline in a concentration of 140 mEq/L would correct the cation deficit, but would further increase the water excess to 5.77 L. Removal of 5.77 L of water would be required in addition to the infusion of 1.47 L of isotonic saline. Signs of hypovolemia were not detected clinically in this patient who was treated only with the use of hypertonic dialysate and reduction of his body weight. His $[Na]_s$ was normalized within 4 days.

Finally, the calculated isotonic volume deficit (6.14 L) in patient 5 was much larger than the measured weight deficit of 2.7 kg. Water consumption accounted for the difference between these 2 estimates. Infusion of 6.14 L of 0.140 m saline would increase his body water to 49.93 L from the value of 43.77 L observed during the time of hyponatremia. Thus, infusion of 6.14 L of 0.140 m saline plus removal of 3.44 L of water would be required to correct both the volume deficit and the relative water excess. The patient received 0.154 m saline infusion but no hypertonic dextrose dialysis. Nevertheless $[Na]_s$ was corrected within the next week after resumption of his regular diet.

DISCUSSION

Determination of the frequency of hyponatremia and of each of its 3 categories, euvolemic, hypovolemic and hypervolemic, in PD requires studies in large PD cohorts. The selected cases analyzed in this report indicate that PD patients may develop any of the 3 categories. The clinical evaluation of volume status and the quantitative analysis of excess or deficit of monovalent cations were in agreement, except for patient 4, who had no clinical signs of hypovolemia, but was found to have opposite deviations in body water (increase) and total monovalent cations (decrease). In this case, clinical evaluation had failed to uncover the cation deficit detected by the quantitative analysis.

The agreement between clinical evaluation and the method presented in this report suggests that this method could be used to characterize the fluid status of PD patients with hyponatremia. However, the practical application of the method will need substantiation by further studies. One potential benefit from classification of PD-associated hyponatremia is epidemiologic, i.e. determination of the frequency of various categories of hyponatremia and clarification of the effect of each type of hyponatremia on morbidity and mortality. Adverse influences on PD outcomes have been associated with hypervolemia (21–23). Low-sodium intake, which could cause hypovolemia, has also been associated with high mortality in PD patients (24). Whether the development of hyponatremia in PD patients contributes to the adverse effects of hypervolemia or hypovolemia could be studied by this method.

The main potential benefit of the method presented in this report is its therapeutic application. The classification of hyponatremia can be used to derive specific treatment directions for removal or infusion of water and electrolytes (Figure 1). However, the question of whether this method can be used as a guide to fluid management in PD patients will await prospective trials before a definitive recommendation can be made. The determination of dry weight and of the estimates of body water are the major limitations for practical application of this method.

Unlike hyponatremic patients in the general population, in whom estimates of dry weight are often unavailable, PD patients routinely have dry weight evaluations. However, the determination of dry weight in PD patients, usually based on clinical evaluation, is prone to large errors. The importance of an accurate determination of dry weight for the management of volume issues in PD patients is recognized (21–23). A recent report stressed the need for accuracy in the determination of dry weight in hemodialysis patients (25). The evaluation of hyponatremia and the guidance provided in the choice of the proper therapeutic measures is another potential benefit of accurate dry weight determination in PD patients. To avoid large errors in the calculations of electrolyte and water deviations, dry weight should be determined frequently, particularly in patients with catabolic illnesses. Patient 2 of this report is an example of a potential overestimation of electrolyte and water deficits because of a dry weight determined at a time remote from the episode of hyponatremia.

The estimates of body water are another potential source of error of the method presented. Estimates of body water from anthropometric formulas developed in euvolemic subjects, such as the Watson formula (20) used in this report, have a substantial margin of error even in the face of euvolemia. In patients with volume abnormalities, these formulas systematically underestimate the magnitude of volume excesses or deficits (26,27). The calculation of body water at the time of hyponatremia as the sum of body water at dry weight, which is presumably not associated with volume abnormalities, plus or minus the weight difference between the weight at the time of hyponatremia and the dry weight, may prevent these systematic errors (26–28). Accuracy of the determination of dry weight is of paramount importance in the prevention of these systematic errors. Bedside determination of body water by a method that is both more accurate than estimates from anthropometric formulas and clinically available, such as bioelectrical impedance analysis,

could improve the accuracy of the method presented in this report.

Another limitation of the method presented is that it does not distinguish deficits of sodium from deficits of potassium. Potassium deficits contributing to hyponatremia are difficult to predict because they come, largely, from the intracellular compartment and may be poorly reflected in $[K]_s$. Calculated cation deficits should be replaced by saline infusions, while administration of potassium compounds to patients with combined hyponatremia and hypokalemia should be cautiously carried out. Monitoring of $[K]_s$ during potassium replacement in patients on PD is critical. It is important to regard the administered potassium as a part of the monovalent cation administered when PD-associated hyponatremia is corrected by the administration of saline plus potassium salts.

Because of the large potential margin of error in the calculations of dry weigh and body water, relatively small estimates of monovalent cation excess or deficit in patients without clinical manifestations suggesting hypervolemia or hypovolemia may not be valid. However, small deviations may also have limited clinical importance. Large excesses or deficits of monovalent cations or water should be detectable by the method presented here. Nevertheless, monitoring of the clinical status of the patients and of appropriate laboratory tests, including frequent determinations of $[Na]_s$ and $[K]_s$, should always accompany treatment measures based on the present method.

One final point of interest is that the calculations for patient 1 shown in Table 2 could be done also at the time of presentation of hyperglycemia using as euglycemic $[Na]_s$ a value corrected for the degree of hyperglycemia. Katz (29) predicted that $[Na]_s$ declines by 1.6 mEq/L for each 5.6 mmol/L (100 mg/dL) increment in $[Glu]_s$. Using Katz's prediction, Al-Kudsi *et al.* (30) proposed the following calculation of $[Na]_s$ at hyperglycemia corrected to a $[Glu]_s$ of 5.6 mmol/L (100 mg/dL):

$$Corrected\ [Na]_s = Actual\ [Na]_s + 1.6 \times \frac{[Glu]_s - 100}{100}$$

where $[Glu]_s$ is in mg/dL. This formulation computes a corrected $[Na]_s$ value of 120.7 mmol/L in patient 1. Calculations using this corrected $[Na]_s$ value provide almost identical results with those obtained by using the $[Na]_s$ value of 121 mEq/L obtained after correction of this patient's hyperglycemia.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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