Review

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Sodium Balance in Maintenance Hemodialysis

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Sodium is the principal solute in the extracellular compartment and the major component of serum osmolality. In normal persons in the steady state, sodium homeostasis is achieved by a balance between the dietary intake and the urinary output of sodium, whereas in intermittent hemodialysis patients, sodium balance depends on dietary intake and sodium removal during hemodialysis. Thus, the main goal of hemodialysis is to remove precisely the amount of sodium that has accumulated during the interdialytic period. Sodium removal during hemodialysis occurs via convective (~78%) and diffusive losses (~22%) between dialysate and plasma sodium concentration. The latter (the sodium gradient) is an important factor in the 'fine tuning' of sodium balance during intermittent hemodialysis. Most use fixed dialysate sodium concentrations, but each patient has his/her own plasma sodium concentrations pre-hemodialysis, which are quite reproducible and stable in the long-term. Thus, in many patients, a fixed dialysate sodium concentration will cause a persistent positive sodium balance during dialysis, which could possibly cause increased thirst, interdialytic weight gain, and mortality. Several methods will be discussed to reduce positive sodium balance, including sodium alignment.

Key Words: Dialysate; Sodium; Balance; Hemodialysis

Introduction

The primary role of maintenance hemodialysis (HD) is the extracellular fluid volume (ECV) balance which is made possible by the neutral sodium balance between interdialytic sodium intake and sodium removal during HD sessions[1]. However, current HD still uses high-sodium bicarbonate dialysate to reduce dialysis hypotension, which is unphysiologic and causes ECV expansion and hypertension[2]. To achieve zero dialysate-to-plasma sodium gradient, several methods have been proposed. In this article, the author discusses new aspects of sodium balance in HD patients and sodium alignment, the recently introduced practical method of neutral sodium balance during HD session.

Sodium balance in healthy individuals and in chronic kidney diseases patients

In healthy persons, sodium (Na^+) and water input through the gut are precisely balanced by kidney Na^+ and water output, thus the size of ECV is maintained by adjusting daily Na^+ excretion between virtually zero to several hundreds of millimoles per day[3]. In populations where Na^+ intake is below 50 mmol/day, there is no hypertension and no progressive rise in blood pressure (BP) with age. However, in a populations where Na^+ intake is 50 to 100 mmol/day, there is a steep rise in the percentage of hypertensive individuals to about 25%[4]. Thus, dietary intake of about 6 g of salt (NaCl) per day appears reasonable in individuals with normal renal function. However, natriuresis, the only physiological exit route for Na^+, is

often challenged by kidney disease, and as renal failure worsens, the ability of the kidneys to excrete Na^+ decreases, salt sensitivity increases, and the incidence of hypertension increases[3]. About 90% of end-stage renal disease (ESRD) patients are hypertensive at the start of dialysis and Na^+ is the dominant factor of hypertension in ESRD[5].

In the classical two-compartment model of Na^+ balance, Na^+ is the main solute of the ECV and potassium (K^+) is the main solute of intracellular volume. Although the cell membrane is permeable to both Na^+ and K^+, these ions are able to act as effective osmoles because they are restricted to their respective compartments by the activity of the Na^+-K^+-ATPase pump in the cell membrane[6]. However, recent data suggest there is a third compartment of Na^+ balance and that large amounts of Na^+ can be accumulated without accompanying water retention in this compartment by two mechanisms, that is an osmotically inactive Na^+ storage mechanism (as characterized by a cation excess relative to water) and an osmotically neutral cation exchange mechanism (as characterized by the replacement of K^+ ions with Na^+ ions)[6]. Animal experiments suggest that the skin is an important osmotically inactive Na^+ reservoir in rats. As compared with rats on a 0.1% NaCl diet, skin Na^+ content in rats fed an 8% NaCl diet were increased by ~35-45%[7]. Furthermore, increases in the skin Na^+ content coincided with only moderate or no increase in skin water content, indicating water-free Na^+ retention, which with a high-salt diet is not paralleled by skin K^+ loss[8]. The skin is a highly vascularized organs and consists mainly of extracellular matrix of high glycosaminoglycan (GAG) content. Osmotically inactive Na^+ storage in skin is accompanied by specific changes in extracellular GAG polymerization and sulfation. In rats, a high salt diet was found to lead to increased skin GAG content[9] and pronounced skin GAG sulfation[8], which resulted in an increase in negative GAG charge density. Water-free Na^+ retention also appears to be essential for the maintenance of body fluid balance in experimental mineralocorticoid excess. Deoxycorticosterone acetate treatment, an animal model of mineralocorticoid induced salt-sensitive hypertension, led to Na^+ excess in rats, and increased total body Na^+ contents by 40-50% within 5 weeks[10], but only ~20% of the Na^+ accumulated led to volume retention. In fact, only moderate increases in total body water content were observed despite massive Na^+ retention. The remainder of the Na^+ load was accumulated by osmotically neutral Na^+/K^+ exchange, or by osmotically inactive Na^+ storage without accompanying water retention. Water-free Na^+ accumulation by osmotically inactive Na^+ storage was found in skin, whereas skeletal muscle exhibited osmotically neutral Na^+/K^+ exchange.

Then, what is the role of the third compartment of Na^+ balance ? First, it contributes to the persistence of hypertension. According to Guyton's experiment, acute volume loading caused increases in ECV and blood volume, increased cardiac output, slightly decreased total peripheral resistance, and elevated BP in dogs with a 70% reduction of kidney mass[11]. Within the few days following isotonic saline infusion, ECV, blood volume, and cardiac output decreased, but total peripheral resistance increased and BP remained elevated[12]. Either excessive Na^+ intake or Na^+ retention by the kidneys and the consequent tendency toward plasma volume expansion lead to the release of endogenous ouabain (EO), probably from the hypothalamus. The Na^+, K^+-ATPase pumps in vascular smooth muscle cells (VSMCs) are inhibited by increases in plasma EO, which results in an elevation of local Na^+ in the submembrane area. This produces electrogenic depolarization of VSMCs and facilitates Ca^{2+} entry through Na^+/ Ca^{2+} exchanger. The resulting rise in cytosolic Ca^{2+} concentration should promote vasoconstriction and, in vivo, elevate BP. Second, the third compartment seems to be related to delayed decreases in BP after ECV normalization (the lag phenomenon). Water-free Na^+ storage in VSMCs may be very slowly relieved during HD because of the restored Na^+, K^+- ATPase activity. This compartment may also be associated with a slow release of osmotically inactive Na^+ from bones, cartilages, dense

connective tissue, and the interstitial matrix lining the intimal surfaces of blood vessels containing proteoglycans and glycosaminoglycans[12].

Sodium balance in hemodialysis patients

The preservation of Na^+ balance (ECV balance) is a key task of renal replacement therapy. Assuming that chronic HD patients are functionally anephric with no gastrointestinal disease leading to volume losses, Na^+ balance is primarily dependent on two factors: dietary salt intake and Na^+ removal during HD[1]. During intermittent HD, Na^+ removal depends primarily on convective losses (~78 %) rather than on diffusive losses (~22%)[13]. Nevertheless, diffusive Na^+ loss has an important role in the fine tuning of Na^+ balance in chronic HD. However, optimal dialysate sodium (DNa^+) concentration differs between individuals and largely depends on the Na^+ gradient, that is, on the difference between dialysate and pre-HD serum Na^+ concentration[14].

From the 1980s, dialysis units have adopted high sodium bicarbonate dialysate, because higher mean (DNa^+) levels reduce dialysis discomfort and the incidences of symptomatic hypotension and disequilibrium[15]. However, high DNa^+ concentrations may lead to positive Na^+ balance and cause fluid overload and hypertension. In general, post-HD serum sodium (SNa^+) exceeds pre-HD values by 2 meq/L to 4 mEq/L, implying that HD removes a hyponatremic ultrafiltrate of plasma water and the patient's exchangeable Na^+ pool is incompletely depleted of excess Na^+[15]. This subtle failure to achieve neutral Na^+ balance during HD increases plasma Na^+ activity and may result in a cumulative total body Na^+ expansion, excessive thirst, increased interdialytic weight gain, and the recrudescence of hypertension in sensitive individuals[16]. Furthermore, each dialysis patient has a unique set point for SNa^+[17], which is stable over long-term observations[18] and actively defended[19]. These findings increase the importance of DNa^+ individualization to achieve a neutral Na^+ balance[20].

Indeed, in one study, mean pre-HD SNa^+ concentration and Na^+ gradient were 136.7±2.9 mmol/L and 4.6± 4.4 mmol/L, respectively, and 83% of patients had a pre-HD SNa^+ concentration lower than 140 mmol/L[21]. In another, a relationship was found between the Na^+ gradient and the ultrafiltration rate, which indicated higher interdialytic weight gain in a patient with a positive Na^+ gradient[17]. Furthermore, a relationship was found between a positive Na^+ gradient and increased occurrence of intradialytic morbidity[14].

Na^+ modeling may reduce intradialytic hypotension. However, despite the low DNa^+ concentration at the end of HD session, Na^+ modeling is associated with increased interdialytic weight gain and BP because the time-averaged Na^+ concentration is high and results in a high dialysate-to-plasma gradient during most HD sessions[22,23].

Sodium alignment in dialysis center

Current evidence suggest that neutral Na^+ balance should be pursued during HD[1]. The method used to avoid intradialytic Na^+ loading is to lower DNa^+ concentration. Indeed, low DNa^+ concentration have been related to improved volume and BP control, but also to more intradialytic symptoms, such as, cramping and hypotension. An alternative method involves the alignment of DNa^+ and SNa^+ concentration.

Currently, this approach is studying at the dialysis clinic of Renal Research Institute, USA[24]. The preliminary results showed a trend of predialysis weight and blood pressure reduction[24].

However, the application of Na^+ alignment presents several problems[24]. The feasibility of measuring SNa^+ prior to every HD session is an obstacle, though the measurement of conductivity in serum and dialysate as a surrogate of SNa^+ and DNa^+ might offer an alternative to a direct Na^+ measurements[13]. However, this requires the use of additional devices and the relationship between

SNa^+ and conductivity is influenced by many factors such as protein binding and complexation with anions such as sulfate and phosphate[24]. The use of historic values offers a solution to the avoidance of on-site measurement of SNa^+ and conductivity-based surrogates. In Keen et al, the historic value was computed from monthly routine laboratory data for every patient over an observation period ranging from 9 to 16 months[17]. These historic value had a coefficient of variation of only 1.6% for monthly SNa^+ in 100 patients over a period of 12 months[18]. Similarly, Rainmann et al. showed that the mean SNa^+ values of the previous 4 months resulted in accurate predictions with low variability and high reliability[24].

Additional technical and physiological aspects should also be considered. Na^+ migrates from the compartment with the higher concentration to the one with the lower concentration to establish equilibrium. The Gibbs-Donnan effect, which concerns the establishment of electroneutrality, alters this diffusive flux of positively charged Na^+ ions because negatively charged plasma proteins are unable to transit the membrane[25]. This effect, which is quantified using the Donnan coefficient α, has been expressed mathematically as follows[25]: Donnan-coefficient α $= 1.007 - 0.009 \times TP$, where TP is the total protein concentration in g/dL.

In addition, osmotically active Na^+ distributes in plasma water only and plasma contains approximately 94% water and 6% proteins and lipids by volume. Thus, it is crucial to know and understand the methods used for SNa^+ determination. Flame photometry measures total Na^+ in a defined volume, whereas direct potentiometry measures electrically active Na^+ concentrations in plasma water, and thus, resulting values are higher than those obtained by flame photometry[24]. The most commonly used method is indirect ionometry, which involves diluting plasma by 1:20 with buffer. All Na^+ present in the plasma is ionized due to the addition of the buffer, and thus, indirect ionometry results reflects the total concentration of Na^+ in plasma and its values are comparable to those of flame photometry.

When performing Na^+ alignment calculations, void volume, and the Gibbs-Donnan effect may be included. Mathematically, this is done as follows[24,26].

$$S'Na^+ = SNa^+ \times [1.007 - (0.009 \times TP)]/[0.989 - (0.0047 \times TP)]$$

$S'Na^+$: Adjusted Serum Sodium

The adjustment proposed by Gotch et al[26] does not consider the lipid contribution to void volume. Thus, in the presence of hyperlipidemia, the algorithm by Waugh[27] may be more precise.

Na^+ alignment in diabetics is another important topic, as glucose is osmotically active and hyperglycemia shifts water from the intracellular to the extracellular compartment, which reduced SNa^+. Katz proposed a correction factor of -1.6 mEq/L per every 100 mg/dL of glucose above 100 mg/dL[28]. Furthermore, a linear approach in chronic maintenance HD patients suggested a correction factor of -1.5 mEq/L be applied per 100 mg/dL increase in serum glucose[29].

In addition, it is important that dialysis machine be accurately calibrated[24], because the delivery of DNa^+ is controlled by monitoring the conductance of the dialysis fluid, which is a dynamic measurement and does not reflect the absolute value of delivered DNa^+. Accordingly, the quality of DNa^+ delivery must be assured by making regular DNa^+ measurements and by machine calibration.

Unsolved questions

It remains unclear if alignment is beneficial for patients with a SNa^+ higher than DNa^+, particularly with regard to intradialytic morbid events[24]. Even more challenging is the question as to whether severely hyponatremic patients should undergo Na^+ alignment. Yet more questions regarding how to align incident HD patients immediately after initiating dialysis, the effects of seasonality, and the effects of comorbidities remain to be answered. Further-

more, it is not known whether patient-specific Na^+ set points remains constant over years or whether they change with alterations in ECV, comorbid conditions, age, or therapy.

Conclusion

Recent guidelines[30] and reviews[3,31] demonstrate the importance of Na^+ overload caused by hypertonic dialysate in the pathogenesis of HD-related hypertension and excessive interdialytic weight gain. In addition, the demonstration of fixed and individual osmolar set points in HD patients raise the need for DNa^+ individualization. To preserve neutral Na^+ balance in HD patients, several methods have been proposed, including Na^+ alignment, but the prospective long-term studies with larger numbers of patients are needed to apply in clinical practice.

Conflicts of Interest

The author has nothing to disclose.

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