New insights into the pathophysiology of the dysnatremias: a quantitative analysis

Minhtri K. Nguyen and Ira Kurtz
Division of Nephrology, David Geffen School of Medicine at UCLA, Los Angeles, California 90095-1689

Nguyen, Minhtri K., and Ira Kurtz. New insights into the pathophysiology of the dysnatremias: a quantitative analysis. Am J Physiol Renal Physiol 287: F172–F180, 2004; 10.1152/ajprenal.00106.2004.—Recent theoretical considerations have played an important role in advancing our understanding of the physiological mechanisms responsible for perturbing the plasma water sodium concentration ([Na\(^+\)]\(_{pw}\)) in health and disease. Central to these considerations is the original empirical relationship between the [Na\(^+\)]\(_{pw}\) and total exchangeable sodium (Na\(_e\)), total exchangeable potassium (K\(_e\)), and total body water (TBW) initially discovered by Edelman and colleagues (Edelman IS, Leibman J, O’Meara MP, and Birkenfeld LW. J Clin Invest 37: 1236–1256, 1958). The non-zero values of the slope and y-intercept in this equation play a role in modulating the [Na\(^+\)]\(_{pw}\) and in the generation of the dysnatremias. In this review, the pathophysiological mechanisms underlying the generation and treatment of the dysnatremias are analyzed theoretically and quantitatively. Importantly, the non-zero values of both the slope and y-intercept in the Edelman equation result in several theoretical predictions that can be tested experimentally and have been mathematically incorporated into recently derived equations used to analyze both the generation and the optimal treatment of the dysnatremias. In addition, we review current concepts regarding \( I\) the role of Gibbs-Donnan and osmotic equilibrium in the determination of the [Na\(^+\)]\(_{pw}\); \( 2\) the modulating effect of osmotically inactive exchangeable Na\(^+\) and K\(^+\) on the [Na\(^+\)]\(_{pw}\); \( 3\) the effect of glucose on the [Na\(^+\)]\(_{pw}\) as reflected by changes in Na\(_e\), K\(_e\), and TBW as well as changes in several components of the y-intercept resulting from the hyperglycemia; and \( 4\) the complex role of K\(^+\) in modulating the [Na\(^+\)]\(_{pw}\).

ALTERATIONS IN PLASMA Na\(^+\) concentration ([Na\(^+\)]\(_{p}\)) are the most common electrolyte disorders encountered in hospitalized patients (3). An integrated analysis of the major determinants of [Na\(^+\)]\(_{p}\) was first achieved by Deming and Gerbode in 1953 (10). These authors reported that [Na\(^+\)]\(_{p}\) was affected by the mass balance of Na\(^+\), K\(^+\), and H\(_2\)O in patients receiving a mitral valvectomy. Subsequent studies confirmed that in hyponatremic patients, K\(^+\) administration increased [Na\(^+\)]\(_{p}\) (11, 23, 37). In keeping with these observations, Edelman et al. (14) showed empirically that the plasma water Na\(^+\) concentration ([Na\(^+\)]\(_{pw}\)) is related to the total exchangeable Na\(^+\) (Na\(_e\)), total exchangeable K\(^+\) (K\(_e\)), and total body water (TBW) by the following equation:

\[
[Na^+]_{pw} = 1.11(Na_e + K_e)/TBW - 25.6 \quad (1)
\]

This study was the first to demonstrate that the Na\(_e\), K\(_e\), and TBW are the major determinants of the [Na\(^+\)]\(_{pw}\) (14). In considering the pathogenesis of the dysnatremias, the quantitative and physiological significance of the slope (1.11) and y-intercept (−25.6) in this equation have been ignored until recently (21, 25–28). Indeed, the Edelman equation has been assumed to have a slope of one and a y-intercept of zero (18, 31, 32), which has been shown recently to be theoretically impossible (27, 28) (Fig. 1).

SIGNIFICANCE OF THE SLOPE AND Y-INTERCEPT IN THE EDELMAN EQUATION

The slope and y-intercept in the Edelman equation have recently been shown to have quantitative and physiological significance (27, 28). This analysis demonstrates that there are several physiologically relevant parameters determining the magnitude of the slope and y-intercept that independently alter the [Na\(^+\)]\(_{pw}\):

\[
[Na^+]_{pw} = G/O \left(\frac{Na_e + K_e}{TBW}\right) - G/O \left[\frac{(Na_{osm\ inactive} + K_{osm\ inactive})}{TBW}\right] - \frac{(osmol_{ECF} + osmol_{ISF})}{TBW}\left(\frac{[K^+]_{pw} + \frac{osmol_{pw}}{V_{pw}}}{V_{pw}}\right) \quad (2)
\]

where

\[
G = \frac{(V_{pw} + V_{ISF})}{V_{pw} + 0.95 \times V_{ISF}}
\]

Address for reprint requests and other correspondence: M. K. Nguyen, Div. of Nephrology, David Geffen School of Medicine at UCLA, 10833 Le Conte Ave., Rm. 7-155 Factor Bldg., Los Angeles, CA 90095 (E-mail: mnnguyen@mednet.ucla.edu).
pathophysiology of the dysnatremias

DETERMINANTS OF THE SLOPE IN THE EDELMAN EQUATION

The slope of the Edelman equation is represented by the term $G/\bar{G}$ and is a reflection of the osmotic coefficient ($\bar{G}$) and the Gibbs-Donnan effect ($G$) on the $[\text{Na}^+]_{\text{pw}}$ (Eq. 2) (28). It is known that the body fluid compartments are in osmotic equilibrium and that TBW is passively distributed in proportion to osmotic activity. Because each mole of ionic particle does not exert exactly one osmole of osmotic activity due to the electrical interactions between the ions (i.e., the osmotic activity of most ionic particles is slightly <1), the osmotic coefficient $\bar{G}$ in the slope accounts for the effectiveness of $\text{Na}^+$ salts as independent osmotically active particles under physiological conditions (22, 28). Additionally, the term $G$ in the slope is a reflection of the effect of Gibbs-Donnan equilibrium on the $[\text{Na}^+]_{\text{pw}}$. Due to the presence of negatively charged, impermeant proteins in the plasma space, the distribution of $\text{Na}^+$ and its associated anions is altered to preserve electroneutrality in the plasma and interstitial fluid compartments (17, 30). As a result, the $[\text{Na}^+]_{\text{pw}}$ is typically greater than the interstitial fluid $\text{Na}^+$ concentration ($[\text{Na}^+]_{\text{ISF}}$), whereas the plasma water $\text{Cl}^-$ concentration ($[\text{Cl}^-]_{\text{pw}}$) is lower than the interstitial fluid $\text{Cl}^-$ concentration ($[\text{Cl}^-]_{\text{ISF}}$). Second, the term $G$ is also a function of the volumes of the plasma and interstitial fluid ($V_{\text{pw}}$ and $V_{\text{ISF}}$) because the distribution of $\text{Na}^+$ ions between the plasma and interstitial fluid (ISF) at equilibrium will depend on the respective volumes of the plasma and ISF. In other words, there will be more $\text{Na}^+$ ions distributed in the ISF at equilibrium than that in the plasma by virtue of the fact that the $V_{\text{ISF}}$ is much greater than that of the plasma. Third, the term $G$ has an additional independent effect on the $[\text{Na}^+]_{\text{pw}}$ because it is also a determinant of the magnitude of the $y$-intercept. This is not surprising because the components of the $y$-intercept must be similarly affected by the Gibbs-Donnan effect. Specifically, the distribution of non-$\text{Na}^+$ cations and anions between the plasma and ISF, as represented by the terms $\text{osmol}_{\text{ECF}}$, plasma water $\text{K}^+$, and osmol$_{\text{pw}}$, will also be altered by the presence of negatively charged, impermeant plasma proteins. Finally, due to Gibbs-Donnan equilibrium, the total osmolar concentration is slightly greater in the protein-containing plasma compartment; this extra osmotic force from diffusible ions is added to the osmotic forces exerted by the plasma anionic proteins (30, 31). The end result of the Gibbs-Donnan effect is that more water moves into the protein-containing plasma compartment.

\[ \bar{G} = \text{average osmotic coefficient of } \text{Na}^+ \text{ salts}; \ 0.95 = \text{Gibbs-Donnan ratio for the distribution of univalent cations between the plasma and interstitial fluid}; \ G = \text{Gibbs-Donnan effect}; V_{\text{pw}} = \text{plasma water volume}; \ V_{\text{ISF}} = \text{interstitial fluid volume}; \ \text{Na}_{\text{osm inactive}} = \text{osmotically inactive } \text{Na}^+; \ K_{\text{osm inactive}} = \text{osmotically inactive } \text{K}^+; \ \text{osmol}_{\text{ECF}} = \text{osmotically active, extracellular non-} \text{Na}^+ \text{ and non-K}^+ \text{ osmoles}; \ \text{osmol}_{\text{pw}} = \text{osmotically active, plasma water } \text{Na}^+ \text{ concentration}; \ K_{\text{pw}} = \text{plasma water K}^+ \text{ concentration}; \ \text{and osmol}_{\text{pw}} = \text{osmotically active, plasma water non-} \text{Na}^+ \text{ non-K}^+ \text{ osmoles.} \]
than would be predicted on the basis of the protein concentration alone (30, 31).

DETERMINANTS OF THE $y$-INTERCEPT IN THE EDELMAN EQUATION

There are several physiologically relevant parameters determining the magnitude of the $y$-intercept which independently modulate the $[Na^+]_{pw}$, 1) osmotically inactive Na$_e$ and K$_e$; 2) [K$^+$_$_{pw}$]; 3) intracellular and extracellular osmotically active non-Na$^+$ and non-K$^+$ osmoles; and 4) plasma osmotically active non-Na$^+$ and non-K$^+$ osmoles (27, 28). We now address the role of each of these parameters in modulating the $[Na^+]_{pw}$.

\[
\left( Na_{osm\ inactive} + K_{osm\ inactive} \right)/TBW
\]

There is convincing evidence for the existence of an osmotically inactive Na$^+$ and K$^+$ reservoir that does not contribute to the distribution of water between the extracellular and intracellular spaces (6, 7, 12–14, 19, 33–35). It has been shown that Na$_e$, in bone and a portion of intracellular K$^+$ are bound and are, therefore, osmotically inactive (7, 12–14). Similarly, in the syndrome of inappropriate antidiuretic hormone secretion (SIADH), the quantities of Na$^+$ lost and H$_2$O retained are insufficient to account for the magnitude of the observed reduction in $[Na^+]_{pw}$ in severely hyponatremic patients (6, 33). This discrepancy has been attributed to loss or inactivation of osmotically active solute. The mechanism of the inactivation of osmotically active solute is unclear. However, it is known that the osmotic inactivation of Na$_e$ in SIADH is reversible (29). Indeed, Nolph and Schrier (29) provided evidence for the reactivation of osmotically inactive Na$^+$ with water restriction in SIADH.

More recently, Heer et al. (19) demonstrated positive Na$^+$ balance in healthy subjects on a metabolic ward without increases in body weight, expansion of the extracellular space, or $[Na^+]_p$. These authors, therefore, suggested that there is osmotic inactivation of Na$_e$. Similarly, Titze et al. (35) reported Na$^+$ accumulation in an osmotically inactive form in human subjects in a terrestrial space station simulation study and suggested the existence of an osmotically inactive Na$^+$ reservoir that exchanges Na$^+$ with the extracellular space. Titze et al. (34) also showed that salt-sensitive Dahl rats (which developed hypertension if fed a high-sodium diet) were characterized by a reduced osmotically inactive Na$^+$ storage capacity compared with Sprague-Dawley rats (which developed hypertension if fed a high-sodium diet) were characterized by a reduced osmotically inactive Na$^+$ storage capacity compared with Sprague-Dawley rats, thereby resulting in fluid accumulation and high blood pressure. Together, these findings provide convincing evidence for the existence of an osmotically inactive Na$^+$ and K$^+$ reservoir. The inactivation of Na$_e$ and K$_e$ is, therefore, accounted for quantitatively by the osmotically inactive Na$_e$ and K$_e$ term in the $y$-intercept.

$K_e$ and $[K^+]_{pw}$

According to Eq. 2, both the $K_e$ and the $[K^+]_{pw}$ must independently affect the $[Na^+]_{pw}$. Indeed, the effect of $K^+$ on the $[Na^+]_{pw}$ differs depending on the distribution of $K^+$ in the body fluid compartments (26, 28). Because $K^+$ is as osmotically active as Na$^+$, interstitial and intracellular $K^+$ will tend to increase the $[Na^+]_{pw}$ by promoting the movement of water from the plasma space into the intracellular space (ISF) and intracellular compartment (ICF), respectively. In contrast, the presence of plasma water K$^+$ results in the shift of water from the ICF and ISF to the plasma compartment, thereby lowering the $[Na^+]_{pw}$. Quantitatively, K$_e$ will have a net incremental effect on the $[Na^+]_{pw}$ because the majority of K$^+$ ions are in the intracellular and interstitial compartments, and therefore the effect of K$^+$ in these latter compartments will predominate.

$\frac{(Osmol_{ECF} + Osmol_{ICF})/TBW \times Osmol_{pw}/V_{pw}}{[Na^+]_{pw}}$

Because TBW is passively distributed in proportion to osmotic activity, the presence of osmotically active non-Na$^+$ and non-K$^+$ osmoles will also have a modulating effect on the $[Na^+]_{pw}$. The presence of osmotically active, non-Na$^+$ and non-K$^+$ osmoles in the intracellular compartment (osmol_{ICF}) will tend to increase the $[Na^+]_{pw}$ by promoting the osmotic shift of water from the plasma space into the intracellular compartment. Similarly, the presence of osmotically active, non-Na$^+$ and non-K$^+$ osmoles in the plasma space (osmol_{pw}) will promote a water shift from the ISF and intracellular compartment to the plasma space, thereby lowering the $[Na^+]_{pw}$. Because the osmotically active, non-Na$^+$ and non-K$^+$ osmoles in the extracellular compartment (osmol_{ECF}) include both osmol_{ISF} and osmol_{pw}, osmol_{ECF} will have a net effect of increasing the $[Na^+]_{pw}$ because only one-fifth of the extracellular fluid (ECF) is confined to the plasma space.

EFFECT OF HYPERGLYCEMIA ON THE $[Na^+]_p$

In the setting of hyperglycemia, changes in the $[Na^+]_p$ result not only from the dilutional effect of hyperglycemia induced by the translocation of water but also to changes in the mass balance of Na$^+$, K$^+$, and TBW. Previously, it has been shown that there is an expected decrease of 1.6 meq/l in the plasma $[Na^+]$ for each 100 mg/dl increment in the plasma glucose concentration, assuming no change in the mass balance of Na$^+$, K$^+$, and H$_2$O (20). To predict the effect of changes in the Na$_e$, K$_e$, and TBW as well as the dilutional effect of hyperglycemia on the plasma Na$^+$ concentration ($[Na^+]_p$) attributable to the osmotic shift of water, the $[Na^+]_p$ can be predicted from the following equation (27):

$$[Na^+]_p = 1.03(\text{Na}_e + K_e)/TBW \times 23.8 - (1.6/100)([\text{glucose}] - 120).$$

Therefore, the $y$-intercept is not constant in hyperglycemia-induced dilutional hyponatremia resulting from the translocation of water and will vary directly with the plasma glucose concentration (27) (Fig. 3). The $y$-intercept changes due to simultaneous alterations in three of the four physiological parameters. First, hyperglycemia results in an increase in the ratio (osmol_{ECF} + osmol_{ICF})/TBW, which accounts for the hyperglycemia-induced increase in total body osmolality. This ratio increases because hyperglycemia increases the osmol_{ECF} term, whereas the TBW remains unchanged. In the hyperglycemia-induced osmotic shift of water from the intracellular compartment to the extracellular space, the TBW remains constant because the change in intracellular volume ($\Delta V_{ICF}$) is
Fig. 3. Dependence of the y-intercept on the plasma glucose concentration calculated according to plasma Na⁺ concentration ([Na⁺]ₚw) = 1.03(Naₑ + Kₑ)/TBW − 23.8 − (1.6/100)([glucose] − 120). An increase in the plasma glucose concentration results in a predictable increase in the magnitude of the y-intercept, thereby decreasing the [Na⁺]ₚw (mmol/l). Top line: glucose 120 mg/dl; middle line: glucose 500 mg/dl; bottom line: glucose 1,000 mg/dl.

equal to the change in extracellular volume (ΔVₑCF). Second, the [K⁺]ₚw will also be affected by the hyperglycemia-induced osmotic shift of water as well as the magnitude of subsequent cellular K⁺ efflux induced by the decrease in [K⁺]ₚw and hyperosmolality. Finally, the plasma water concentration of osmotically active non-Na⁺ and non-K⁺ osmoles represented by the term osmolₑCF/¹ₑCF increases in hyperglycemia, thereby lowering the [Na⁺]ₚw by promoting the osmotic movement of water into the plasma space.

K⁺ AND [Na⁺]ₚw

In addition to the differential effects of K⁺ on the [Na⁺]ₚw discussed earlier, previous studies have invoked a role for direct cellular Na⁺ uptake (to replace intracellular K⁺) as a mechanism for the modulation of [Na⁺]ₚw during hypokalemia resulting from negative K⁺ balance (15, 16, 23). Indeed, the concept that a deficit of intracellular K⁺ may result in the entry of Na⁺ into cells to restore electroneutrality is supported by the finding of an increase in non-extracellular Na⁺ and increased ratio of non-extracellular Na⁺ to Naₑ in patients with diuretic-induced hyponatremia (15). However, the cellular uptake of extracellular Na⁺ per se cannot be responsible for the depression of the [Na⁺]ₚw in patients with hypokalemia due to the negative mass balance of K⁺ (26). The cellular uptake of extracellular Na⁺ without concomitant K⁺ exit will not result in a fall in the [Na⁺]ₚw because osmotic equilibrium must be restored by a shift of extracellular water into the cells, thereby raising the [Na⁺]ₚw to normal. This is demonstrated quantitatively by the fact that the cellular uptake of extracellular Na⁺ without concomitant cellular K⁺ efflux will not change the ratio (Naₑ + Kₑ)/TBW or any other terms in Eq. 2. In fact, from the standpoint of the [Na⁺]ₚw, it is irrelevant whether Na⁺ is restricted to the intracellular or extracellular compartments. Intracellular Na⁺, which is as osmotically active as intracellular K⁺, acts to raise the [Na⁺]ₚw by promoting the shift of water from the ECF into the ICF. Similarly, interstitial Na⁺ will also cause a shift of water from the plasma space into the interstitial space, thereby increasing the [Na⁺]ₚw.

Although cellular Na⁺ influx per se will not alter the [Na⁺]ₚw, the cellular loss of K⁺ accompanied by an equimolar Na⁺ influx will result in a decrement in the [Na⁺]ₚw (26). Because intracellular K⁺ is replaced by extracellular Na⁺ in this scenario, there will be no change in the ratio (Naₑ + Kₑ)/TBW. However, the equimolar exchange of cellular K⁺ for Na⁺ will lead to an increase in the [K⁺]ₚw term and therefore, according to Eq. 2, [Na⁺]ₚw must decrease. Because K⁺ is as osmotically active as Na⁺, the increase in plasma K⁺ obligates the retention of water in the plasma space, thereby diluting the [Na⁺]ₚw. Specifically, the reason for the decrease in the [Na⁺]ₚw is not that Na⁺ enters the ICF per se but rather that K⁺ efflux into the ECF prevents water from entering the ICF with Na⁺, resulting in a dilution of the [Na⁺]ₚw. Finally, regardless of the mechanisms of cellular K⁺ efflux, it is important to appreciate that the flux of K⁺ into the plasma space lessens the magnitude of the hypokalemia. However, because cellular K⁺ efflux ameliorates the hypokalemia, as [K⁺]ₚw increases, the magnitude of water flux out of the plasma space will diminish, resulting in a decrease in [Na⁺]ₚw.

In addition to the potential role for direct cellular Na⁺ uptake replacing intracellular K⁺ as a mechanism for ameliorating hypokalemia, cellular K⁺ efflux can also potentially be accompanied by H⁺ influx and/or cellular anion efflux (24, 31). The mechanisms of cellular K⁺ loss will affect the (osmolₑCF + osmolₑICF)/TBW term and, therefore, the [Na⁺]ₚw differently (26). For instance, H⁺ that enters cells in exchange for K⁺ is buffered predominantly by intracellular proteins and HCO₃⁻. When H⁺ entering cells binds to intracellular proteins, the total number of osmotically active, intracellular non-Na⁺ and non-K⁺ particles remains constant since H⁺ + Prot → HProt. Specifically, this reaction does not lead to a change in the osmolₑCF term. The cellular efflux of K⁺ and subsequent urinary K⁺ loss, however, will result in the loss of osmotically active K⁺ particles, which will be reflected in the Kₑ term. Although this cellular K⁺ loss is accompanied by the excretion of extracellular Cl⁻ in the urine, there will be no change in the quantity of osmotically active, extracellular non-Na⁺ and non-K⁺ particles (osmolₑCF) because the H⁺ ions entering the cells are produced along with HCO₃⁻ in the ECF by the following reaction: CO₂ + H₂O → H₂CO₃ → H⁺ + HCO₃⁻. In other words, the loss of extracellular Cl⁻ is equivalent to the gain in HCO₃⁻ in the ECF. Therefore, when H⁺ entering cells binds to intracellular proteins, each millimole of cellular K⁺ lost from the body represents a net loss of 1 mmol from the ICF (1 mmol of K⁺) (24).

Alternatively, H⁺ entering the ICF can also bind to a HCO₃⁻ ion according to the following reaction: H⁺ + HCO₃⁻ → H₂CO₃ → CO₂ + H₂O. The effect of this reaction is to decrease the non-Na⁺ and non-K⁺ osmoles in the ICF. The concomitant cellular loss of K⁺ will result in the loss of 2 mmol of osmotically active particles (1 mmol of HCO₃⁻ and 1 mmol of K⁺) from the ICF per mmol of cellular K⁺ lost from the body. The loss of intracellular HCO₃⁻ (excreted as CO₂) will result in a decrease in osmolₑCF, and, therefore, the (osmolₑCF + osmolₑICF)/TBW term. The subsequent cellular...
K+ loss along with extracellular Cl− in the urine, however, will not result in a change in the quantity of osmotically active, extracellular non-Na+ and non-K+ particles (osmolECF) because the H+ ions entering the cells are produced along with HCO3− in the ECF by the reaction CO2 + H2O \rightarrow H2CO3 \rightarrow H^+ + HCO_3^−.

If total body K+ loss results from cellular K+ loss accompanied by cellular anion loss, the nature of the anion will determine whether there will also be a reduction in the (osmolECF + osmolICF)/TBW term due to a decrease in the quantity of osmotically active, intracellular non-Na+ and non-K+ osmotes (osmolICF). As previously discussed, the majority of K+ loss originates from the ICF because the quantity of exchangeable K+ in the ICF, ISF, and plasma space in an average 70-kg man is 3.750 mmol (150 mmol/l × 25 liters), 62 mmol (4.4 mmol/l × 14 liters), and 14 mmol (4.6 mmol/l × 3 liters), respectively. Therefore, K+ is lost from the cells along with an intracellular anion from the ICF to the ECF and subsequently is excreted in the urine. For instance, for each millimole of cellular K+ loss along with intracellular phosphate in the urine, the net loss is only 1 mmol from the ICF (1 mmol of K+ because phosphate is derived from an intracellular macromolecule such as RNA (24). Therefore, there will be no change in the (osmolECF + osmolICF)/TBW term in this setting. On the other hand, the loss of cellular K+ along with intracellular Cl− (31) in the urine will result in a net loss of 2 mmol from the ICF (1 mmol of K+ and 1 mmol of Cl−) and a decrease in the osmolICF term. Hence, the mechanisms by which K+ is lost from the cells will determine the magnitude of change in the [Na+]pw (26). In other words, the magnitude of the reduction in the quantity of osmotically active, intracellular non-Na+ and non-K+ osmotes (osmolICF) will determine the magnitude of the decrease in the [Na+]pw due to the shift of water out of the cells.

Negative ECF K+ balance is typically accompanied by negative Cl− balance. Cl− anions accompanying interstitial and plasma K+ loss will lead to a reduction in the (osmolECF + osmolICF)/TBW term due to a decrease in the quantity of osmotically active, extracellular non-Na+ and non-K+ osmotes (osmolECF). The effect of interstitial anion loss on the [Na+]pw differs from that of plasma anion loss. The loss of anions from the ISF will induce the movement of water from the interstitial space into the plasma space, thereby lowering the [Na+]pw. On the other hand, plasma anion loss will raise the [Na+]pw because there are fewer osmotically active, plasma non-Na+ osmotes diluting the [Na+]pw. Because only one-fifth of the ECF is confined to the plasma space (31), quantitatively the loss of interstitial and plasma anions (osmolICF) accompanying extracellular K+ loss will result in a net decrement in the [Na+]pw.

LESSONS LEARNED FROM THE EDELMAN EQUATION IN ANALYZING THE GENERATION OF THE DYSNATREMIAS

In analyzing the mechanisms responsible for the generation of the dysnatremias, various approaches have been reported, including measurements of plasma and urine osmolality, free water clearance (FWC), electrolyte free water clearance (EFWC), and tonicity balance (8, 24, 31, 32). Comparison of the urinary to plasma osmolality is frequently performed in patients with dysnatremias to determine whether the kidney is excreting dilute or concentrated urine (31, 32). However, such an analysis fails to account for both the input and non-urinary output of H2O, Na+, and K+, and it cannot quantitatively predict the magnitude of the change in [Na+]pw in a given patient (21). Moreover, urea, which is an ineffective osmole, is included in the osmolality measurement of urine and blood. The FWC and EFWC analyses suffer from similar difficulties in that one cannot accurately and quantitatively predict the magnitude of the expected change in [Na+]pw as well (21). It has been suggested that the EFWC analysis is superior to the calculation of FWC to document the role of the kidney in generating the dysnatremias, because the EFWC takes into consideration the fact that urea is an ineffective osmole. However, the EFWC is erroneous in its prediction of the direction of change in the [Na+]pw because one ignores the input and nonrenal output of Na+, K+, or H2O (21). Finally, a tonicity balance approach has been proposed wherein the mass balance of electrolytes and water is considered (8). However, this approach also suffers from several disadvantages. The [Na+]p is assumed to equal (Na+ + K+)/TBW, ignoring the fact that Edelman et al. (14) demonstrated empirically that the [Na+]pw is related to the Na+, K+, and TBW according to Eq. 1. By assuming that the [Na+]p is exactly equal to the ratio (Na+ + K+)/TBW, the tonicity balance approach cannot account for 1) the net depressive effect of osmotically inactive Na+ and K+, [K+]pw, and osmotically active, non-Na+ and non-K+ osmotes on the [Na+]pw; 2) the effect of ionic interactions between Na+ and its associated anions under physiological conditions (as reflected by the average osmotic coefficient of Na+ salts); and 3) the incremental effect of the Gibbs-Donnan effect (G) on the [Na+]pw (28). By ignoring the y-intercept, the tonicity balance approach also cannot simultaneously and quantitatively incorporate the role of hyperglycemia in its conceptual framework (21). Finally, the tonicity balance approach considers the mass balance of electrolytes and water separately. However, patients usually have simultaneous changes in these parameters, necessitating both mathematically and conceptually a single formula that incorporates both the mass balance of Na+ + K+ (EmB), and the mass balance of H2O (VMB), as well as the dilutional effect of hyperglycemia on the [Na+]pw. This is particularly important in analyzing the generation of hyponatremia in patients with ketoacidosis who have simultaneous changes in the mass balance of Na+, K+, and H2O, and transcellular H2O shifts associated with hyperglycemia (4, 27).

Earlier analyses of the generation of the dysnatremias did not incorporate mathematically in a single equation, the known factors that account quantitatively for changes in the [Na+]pw. Recently, the goal of incorporating the known factors responsible for generating the dysnatremias into a single equation has been accomplished (21):

\[
[Na^+]_{pw2} = \frac{([Na^+]_{pw1} + y_1)TBW_1 + 1.03 \times E_{MB}}{TBW_1 + V_{MB}} - y_2 \tag{3}
\]

where
\[
y = 23.8 + (1.6/100) ([G] - 120)
\]
\[
[E] = [Na^+ + K^+]
\]
Pathophysiology of the Dysnatremias

**Table 1. Pathophysiology of hyponatremia**

<table>
<thead>
<tr>
<th>Classification of Hyponatremia</th>
<th>VMB</th>
<th>EMB</th>
<th>Relative Effects of EMB and VMB on [Na⁺]ₚ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic</td>
<td>Negative</td>
<td>Negative</td>
<td>EMB &gt; VMB</td>
</tr>
<tr>
<td>Euvolemic</td>
<td>Positive</td>
<td>Negligible</td>
<td>VMB &gt; EMB</td>
</tr>
<tr>
<td>Hypervolemic</td>
<td>Positive</td>
<td>Positive</td>
<td>EMB &gt; VMB</td>
</tr>
</tbody>
</table>

VMB represents the mass balance of H₂O; EMB represents the mass balance of Na⁺ + K⁺; [Na⁺]ₚ = plasma water Na⁺ concentration.

On the other hand, in euvolemic hyponatremia, the positive VMB is the cause of the decrease in [Na⁺]ₚ, whereas the EMB is negligible in this setting. Similarly, in hypervolemic hyponatremia, the positive VMB is the cause of the hyponatremia. However, in this setting, the positive EMB would tend to raise the [Na⁺]ₚ, but its incremental effect is less than the depressive effect of the positive VMB on the [Na⁺]ₚ.

This type of analysis can also be applied to derive insights into the mechanisms underlying the generation of hypernatremia. In hypovolemic hypernatremia, the negative VMB is the cause of the hypernatremia, whereas the negative EMB in this setting would lower the [Na⁺]ₚ, but its depressive effect is less than the incremental effect of the negative VMB on the [Na⁺]ₚ (Table 2). In these patients, a defect in thirst mechanism or inadequate access to H₂O contributes to the negative VMB. In euvolemic hypernatremia, the negative VMB is also the cause of the hypernatremia, but the EMB is negligible in these patients. Finally, in hypervolemic hypernatremia, it is the positive EMB that is the cause of the hypernatremia (rather than negative VMB); the positive VMB in these patients tends to lower the [Na⁺]ₚ but is not of sufficient magnitude to prevent the [Na⁺]ₚ from increasing. In this setting, the positive VMB is inadequate to correct the hypernatremia due to a defect in thirst mechanism or inadequate access to H₂O.

**Table 2. Pathophysiology of hypernatremia**

<table>
<thead>
<tr>
<th>Classification of Hypernatremia</th>
<th>VMB</th>
<th>EMB</th>
<th>Relative Effects of EMB and VMB on [Na⁺]ₚ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic</td>
<td>Negative</td>
<td>Negative</td>
<td>EMB &gt; VMB</td>
</tr>
<tr>
<td>Euvolemic</td>
<td>Negative</td>
<td>Negligible</td>
<td>VMB &gt; EMB</td>
</tr>
<tr>
<td>Hypervolemic</td>
<td>Positive</td>
<td>Positive</td>
<td>EMB &gt; VMB</td>
</tr>
</tbody>
</table>

Various formulas ([Na⁺] deficit equation, water deficit equation, Androuge-Madias equation, and Barsoum-Levine equation) have been derived to predict the change in [Na⁺]ₚ after an infusion of Na⁺, K⁺, and H₂O (1, 5, 31). Several limitations are inherent in these previous formulas used to predict the effect of a given infusion on the change in [Na⁺]ₚ (Δ[Na⁺]ₚ). For instance, the limitations inherent in the Na⁺ deficit equation include the lack of consideration of 1) changes in TBW with therapy; 2) the effect of K⁺ on the [Na⁺]ₚ; 3) various sources of Na⁺, K⁺, and H₂O input that the patient may be receiving in addition to the chosen infusion; 4) any ongoing urinary, gastrointestinal, and cutaneous losses of water and electrolytes; and 5) the known empirical relationship between the [Na⁺]ₚ, Naₑ, Kₑ, and TBW (Eq. 1). Similarly, the water...
consequence of assuming [Na+]p is equal to the ratio (Na+ + K+)/TBW. Rather, Edelman et al. (14) empirically demonstrated that the [Na+]p (as opposed to [Na+]pl) is equal to 1.11(Na+ + K+)/TBW - 25.6. Like all previous formulas, the Barsoum-Levine equation fails to consider the fact that plasma is 93% water (2, 9), and it cannot account for the quantitative and physiological significance of the slope (1.11) and y-intercept (-25.6) in Eq. I.

Consequently, by ignoring the quantitative significance of the slope and y-intercept in Eq. 1, the Na+ deficit equation, water deficit equation, Androgue-Madias equation, and Barsoum-Levine equation will inaccurately predict the effect of a given infusion on the Δ[Na+]p because the Δ[Na+]p induced by a given mass balance of Na+, K+, and H2O will vary depending on the initial Na+ and K+ (21, 25, 27, 28). As a result, these formulas may lead to significant errors in the predicted Δ[Na+]p.

NEW APPROACHES FOR QUANTITATIVELY PREDICTING THE ROLE OF Na+, K+, AND H2O IN MODULATING THE [Na+]p

The Nguyen-Kurtz formula has recently been derived to accurately determine the amount of a given infusion required to induce a given change in the [Na+]p (25):

\[\text{V}_{\text{IVF}} = \frac{[([\text{Na}]_1 + 23.8) \times \text{TBW} - [([\text{Na}]_2 + 23.8)]}{(\text{TBW} + V_{\text{NET}}) + 1.03}\left(\text{E}_{\text{input}} \times V_{\text{input}} - [E_{\text{output}} \times V_{\text{output}}]\right) + [E_{\text{urine}} + E_{\text{GI}} + E_{\text{sweat}} + E_{\text{insensible}}]
\]

where V = volume; IVF = intravenous fluid; [Na]1 = initial plasma sodium concentration; [Na]2 = target plasma sodium concentration; [E] = [Na+ + K+]; VNET = mass balance of water excluding the volume of IV fluid (V_{IVF}) which is being solved for:

\[V_{\text{NET}} = (V_{\text{oral}} + V_{\text{tube feed}} + V_{\text{TPN}} + V_{\text{oxidation}})
\]

\[E_{\text{input}} \times V_{\text{input}} = [E]_{\text{oral}} \times V_{\text{oral}} + [E]_{\text{tube feed}} \times V_{\text{tube feed}}
\]

\[E_{\text{output}} \times V_{\text{output}} = [E]_{\text{urine}} \times V_{\text{urine}} + [E]_{\text{GI}} \times V_{\text{GI}} + [E]_{\text{sweat}} \times V_{\text{sweat}}
\]

In the derivation of this formula, consideration was given to all the inherent assumptions and limitations of the previous formulas. This formula has several advantages: 1) it accounts for all input and output sources of Na+, K+, and H2O (mass balance) that can result in a Δ[Na+]p; 2) it takes into consideration the fact that plasma is 93% water (2, 9) and that the [Na+]pw = 1.11(Na+ + K+)/TBW - 25.6 (Eq. I); 3) it considers the therapy-induced change in TBW; 4) it is applicable for both hyponatremia and hypernatremia; 5) it calculates directly the amount of the infusion necessary to induce a given Δ[Na+]p; and 6) it may also be used to determine the inappropriateness of the selected fluid prescription in a given clinical situation (25).

In the setting of hyperglycemia, none of the previous formulas is applicable. Recently, we demonstrated that an elevation in blood glucose lowers the [Na+]p because it increases the magnitude of the y-intercept in Eq. 1 in a predictable fashion by increasing the concentration of osmotically active non-Na+ and non-K+ osmoles (21, 27, 28). Accordingly, the y-intercept of 23.8 in the Nguyen-Kurtz formula needs to be replaced by the specific hyperglycemia-modified value in patients with hyperglycemia. During stable hyperglycemia, the Nguyen-
Kurtz formula incorporating the modified y-intercept can be used as a guide to therapy. Although the glucose-induced change in the magnitude of the y-intercept can be determined retrospectively and therefore used in a straightforward manner to quantitatively analyze the generation of the dysnatremias (21), it is impossible to prospectively predict the blood glucose level in any patient. Therefore, blood chemistries need to be measured more frequently as a guide to therapy in those patients who are predicted clinically to have unstable blood glucose levels.

Similarly, the magnitude of the y-intercept in the Edelman equation can theoretically change when there is a major change in any of the other components of the y-intercept. For instance, the y-intercept may potentially change if there is a significant change in the quantity of osmotically inactive Na\textsubscript{e} and K\textsubscript{e} or intracellular osmotically active, non-Na\textsubscript{e} and non-K\textsubscript{e} osmoles. Unfortunately, it is currently not clinically feasible for one to account for these factors prospectively. Moreover, as with all previous formulas, it is important to realize that there may be dynamic changes in the mass balance of Na\textsuperscript{+}, K\textsuperscript{+}, and H\textsubscript{2}O after administration of a given infused. Finally, the accuracy of all current formulas is dependent on an accurate estimate of the TBW. In this regard, an accurate estimate of TBW can be determined by using the regression equations reported by Watson et al. (36).

\[ \Delta[Na^+]_p \text{ INDUCED BY SALINE ADMINISTRATION IN SYMPTOMATIC SIADH} \]

SIADH was first described by Schwartz and Barter in 1957 (33). Since its first description, the pathogenesis and management of this disorder have been well characterized. The primary factor in the pathogenesis of the hyponatremia in SIADH is thought to be water retention rather than cation loss (29). Indeed, Nolph and Schrier (29) demonstrated that the increase in urinary Na\textsuperscript{+} excretion seen with rapid water expansion in SIADH is associated with a reciprocal depression in urinary K\textsuperscript{+} excretion. As a result, the negative Na\textsuperscript{+} balance occurring during the rapid increase in TBW is offset by the positive K\textsuperscript{+} balance such that the net cumulative loss of Na\textsubscript{e} and K\textsubscript{e} is negligible in SIADH. Because water retention rather than cation loss is the main contributor to the development of hyponatremia in SIADH (29), therapeutic maneuvers that primarily result in negative water balance rather than positive Na\textsuperscript{+} balance would be the preferred mode of treatment. Until a vasopressin-receptor antagonist is available for clinical use, water restriction is the mainstay of therapy in asymptomatic SIADH. However, severe, symptomatic hyponatremia due to SIADH often requires the administration of intravenous saline.

All the above formulas are not applicable in predicting the \[ \Delta[Na^+]_p \] in severe symptomatic SIADH in clinical situations where intravenous therapy (hypertonic saline \pm furosemide) is used to increase the \[ [Na^+]_p \] more rapidly than water restriction alone. These formulas cannot be used to predict the effect of a given infusate on the \[ \Delta[Na^+]_p \] in patients with symptomatic SIADH because they fail to consider the neutral solute balance maintained in these patients (25). Indeed, Na\textsuperscript{+} handling and therefore volume regulation are intact in patients with SIADH in the steady state (29, 32). Specifically, in SIADH, solute balance is maintained and the administered Na\textsuperscript{+} and K\textsuperscript{+} are excreted in the urine. Correction of hyponatremia in SIADH, therefore, occurs by attaining negative water balance while maintaining neutral Na\textsuperscript{+} and K\textsuperscript{+} balance. None of the above formulas accounts for the intact Na\textsuperscript{+} handling in SIADH and therefore cannot be utilized in the treatment of this disorder. Consequently, a new formula has recently been derived that is applicable in the treatment of severe symptomatic SIADH requiring intravenous therapy (25):

\[
V_{IVF} = (TBW_t \times (1 - \{([Na]_t + 23.8)/([Na]_t + 23.8)\} + V_{input} - \{[E]_{input} \times V_{input}/([E]_{urine} \times ([E]_{IVF}/[E]_{urine}) - 1)\}
\]

where \( V \) = volume; IVF = intravenous fluid; \([Na]_t \) = initial plasma sodium concentration; \([Na]_2 \) = target plasma Na\textsuperscript{+} concentration;

\[
[E] = [Na^+ + K^+];
\]

\[
[E]_{input} \times V_{input} = [E]_{oral} \times V_{oral} + [E]_{tube \ feed} \times V_{tube \ feed} + [E]_{TPN} \times V_{TPN} + V_{oxidation}
\]

\[
E_{urine} = \text{urinary}[Na^+ + K^+]
\]

**SUMMARY**

The empirical relationship between the \([Na^+]_{pw} \) and \([Na]_e \), \([K]_e \), and TBW discovered by Edelman et al. (14) has played a pivotal role in recent theoretical and quantitative considerations that have advanced our understanding of the physiologically relevant parameters that modulate the \([Na^+]_{pw} \). The non-zero values of the slope and y-intercept in the Edelman equation are a necessary consequence of the effects of the osmotic coefficient (\( \Omega \)) of Na\textsuperscript{+} salts at physiological concentrations and Gibbs-Donnan and osmotic equilibrium. In addition to \([Na]_e \), \([K]_e \), and TBW, the physiological components of the y-intercept in this equation play a role in modulating the \([Na^+]_{pw} \) and in the generation of the dysnatremias. These physiological components that determine the magnitude of the y-intercept and therefore the \([Na^+]_{pw} \) are the osmotically inactive \([Na]_e \), \([K]_{1pw} \), and the osmotically active non-Na\textsuperscript{+} and non-K\textsuperscript{+} osmoles. An appreciation of these parameters is critically important in conceptually understanding the effect of hyperglycemia on the \([Na^+]_{pw} \) and the complex role of K\textsuperscript{+} in modulating the \([Na^+]_{pw} \). These considerations have recently led to the derivation of new formulas for analyzing the generation and treatment of the dysnatremias that can be tested experimentally.

**ACKNOWLEDGMENTS**

This work was supported by the Max Factor Family Foundation, the Richard and Hinda Rosenthal Foundation, and the Fredericka Taubitz fund.

**REFERENCES**

PATHOPHYSIOLOGY OF THE DYSNATREMIAS

Invited Review