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 the Edelman equation are a consequence of the effects of the osmotic coefficient of Na\(^+\) salts at physiological concentrations and Gibbs-Donnan and osmotic equilibrium. Moreover, 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. 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 1) 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:

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

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\(^+\)]\(_{pw}\):

\[
[\text{Na}^+]_{pw} = G/\text{TBW} - G \left(\frac{\left(\text{Na}_e \text{ in active } + \text{K}_e \text{ in active}\right)}{\text{TBW}}\right) - \left(\frac{\text{osmol}_{ECF} + \text{osmol}_{ISF}}{\text{TBW}}\right) + \left(\frac{[\text{K}]_{pw} + \text{osmol}_{pw}}{V_{pw}}\right) \quad (2)
\]

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, 10853 Le Conte Ave., Rm. 7-155 Factor Bldg., Los Angeles, CA 90095 (E-mail: mtknguyen@mednet.ucla.edu).
The slope of the Edelman equation is represented by the y-intercept calculated according to Eq. 1, the slope is a function of the volumes of the plasma and interstitial fluid (V_{pw} and V_{ISF}) because the distribution of 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 Na\(^+\) ions distributed in the ISF at equilibrium than in the plasma by virtue of the fact that the V_{ISF} is much greater than that of the plasma. Third, the term G has an additional independent effect on the [Na\(^+\)]_{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-Na\(^+\) cations and anions between the plasma and ISF, as represented by the terms osmol_{ECF}, plasma water K\(^+\), and osmol_{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.

**DETERMINANTS OF THE SLOPE IN THE EDELMAN EQUATION**

The slope of the Edelman equation is represented by the term G/Ø and is a reflection of the osmotic coefficient (Ø) and the Gibbs-Donnan effect (G) on the [Na\(^+\)]_{pw} (Fig. 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 Ø in the slope accounts for the effectiveness of 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 [Na\(^+\)]_{pw}. Due to the presence of negatively charged, impermeant proteins in the plasma space, the distribution of Na\(^+\) and its associated anions is altered to preserve electroneutrality in the plasma and interstitial fluid compartments (17, 30). As a result, the [Na\(^+\)]_{pw} is typically greater than the interstitial fluid Na\(^+\) concentration ([Na\(^+\)]_{ISF}), whereas the plasma water Cl\(^-\) concentration ([Cl\(^-\)]_{pw}) is lower than the interstitial fluid Cl\(^-\) concentration ([Cl\(^-\)]_{ISF}). Second, the term G is also a function of the volumes of the plasma and interstitial fluid (V_{pw} and V_{ISF}) because the distribution of 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 Na\(^+\) ions distributed in the ISF at equilibrium than in the plasma by virtue of the fact that the V_{ISF} is much greater than that of the plasma.
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\(^+\)]\(\text{pw}\). 1) osmotically inactive Na\(_e\) and K\(_e\); 2) [K\(^+\)]\(\text{pw}\); 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\(^+\)]\(\text{pw}\).

\[
(\text{Na}_{\text{osm inactive}} + \text{K}_{\text{osm inactive}})/\text{TBW}
\]

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\(^+\)]\(\text{pw}\) 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\(^+\)]\(\text{pw}\). 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\(_e\) 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\(_e\) 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\(^+\)]\(\text{pw}\)**

According to Eq. 2, both the K\(_e\) and the [K\(^+\)]\(\text{pw}\) must independently affect the [Na\(^+\)]\(\text{pw}\). Indeed, the effect of K\(^+\) on the [Na\(^+\)]\(\text{pw}\) 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\(^+\)]\(\text{pw}\) by promoting the movement of water from the plasma space into the interstitial 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\(^+\)]\(\text{pw}\). Quantitatively, K\(_e\) will have a net incremental effect on the [Na\(^+\)]\(\text{pw}\) because the majority of K\(^+\) ions are in the intracellular and interstitial compartments, and therefore the effect of K\(^+\) in these latter compartments will predominates.

\[
(\text{Osmol}_{\text{ECF}} + \text{Osmol}_{\text{ICF}})/\text{TBW} \text{ and Osmol}_{\text{pw}}/\text{Osmol}_{\text{pw}}
\]

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\(^+\)]\(\text{pw}\). The presence of osmotically active, non-Na\(^+\) and non-K\(^+\) osmoles in the intracellular compartment (osmol\(_{\text{ICF}}\)) will tend to increase the [Na\(^+\)]\(\text{pw}\) 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 extracellular space (osmol\(_{\text{pw}}\)) will promote a water shift from the ISF and intracellular compartment to the plasma space, thereby lowering the [Na\(^+\)]\(\text{pw}\). Because the osmotically active, non-Na\(^+\) and non-K\(^+\) osmoles in the extracellular compartment (osmol\(_{\text{ECF}}\)) include both osmol\(_{\text{ISF}}\) and osmol\(_{\text{pw}}\), osmol\(_{\text{ECF}}\) will have a net effect of increasing the [Na\(^+\)]\(\text{pw}\) because only one-fifth of the extracellular fluid (ECF) is confined to the plasma space.

**EFFECT OF HYPERGLYCEMIA ON THE [Na\(^+\)]\(\text{pw}\)**

In the setting of hyperglycemia, changes in the [Na\(^+\)]\(\text{pw}\) 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\(^+\)]\(\text{pw}\)) attributable to the osmotic shift of water, the [Na\(^+\)]\(\text{pw}\) can be predicted from the following equation (27):

\[
[\text{Na}^+][\text{pw}] = 1.03(\text{Na}_e + \text{K}_e)/\text{TBW} - 23.8
- (1.6/100)([\text{glucose}] - 120)
\]

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\(_{\text{ECF}}\) + osmol\(_{\text{ICF}}\))/TBW, which accounts for the hyperglycemia-induced increase in total body osmolality. This ratio increases because hyperglycemia increases the osmol\(_{\text{ECF}}\) 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 (\(\Delta V_{\text{ICF}}\)) is
concentration results in a predictable increase in the magnitude of the intercept, thereby decreasing the ratio of extracellular Na\(^+\)/H\(^+\).

Although cellular Na\(^+\) influx per se will not alter the ratio of intracellular Na\(^+\)/K\(^+\), the cellular loss of K\(^+\) accompanied by an equimolar Na\(^+\)/K\(^+\) influx will result in a decrement in the ratio of Na\(^+\)/K\(^+\) (26).

In addition to the differential effects of K\(^+\) on the Na\(^+\)/K\(^+\) discussed earlier, previous studies have invoked a role for K\(^+\) efflux into the ECF prevents water from entering the ICF (24, 31). The mechanisms of cellular K\(^+\) loss will affect the (osmol\(_{\text{ECF}}\) + osmol\(_{\text{ICF}}\))/TBW term and, therefore, the ratio of Na\(^+\)/K\(^+\) differently (26). For instance, H\(^+\) that enters cells in exchange for K\(^+\) is buffered predominantly by intracellular proteins and HCO\(_3^-\). 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\(^+\) buffered by intracellular proteins and osmol\(_{\text{ICF}}\), the increase in plasma K\(^+\) will affect the ratio of non-extracellular Na\(^+\) to Na\(^+\) in patients with diuretic-induced hyponatremia (15). However, the cellular uptake of extracellular Na\(^+\) per se cannot be responsible for the depression of the ratio of non-extracellular Na\(^+\) to Na\(^+\) in patients with hyperglycemia 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 ratio of extracellular Na\(^+\) to Na\(^+\) because the osmotic equilibrium must be restored by a shift of extracellular water into the cells, thereby raising the ratio of extracellular Na\(^+\) 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 of extracellular Na\(^+\) to any other terms in Eq. 2. In fact, from the standpoint of the ratio of extracellular Na\(^+\), 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 ratio of Na\(^+\) to 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 ratio of Na\(^+\) to.

In addition to the differential effects of K\(^+\) on the ratio of extracellular Na\(^+\) to Na\(^+\) discussed earlier, previous studies have invoked a role for cellular K\(^+\) efflux into the ECF prevents water from entering the ICF with Na\(^+\) efflux and K\(^+\) influx replaced intracellular K\(^+\) and non-K\(^+\) particles (osmol\(_{\text{ECF}}\)) because the H\(^+\) ions entering the cells are produced along with HCO\(_3^-\) in the ECF by the following reaction: CO\(_2\) + H\(_2\)O → H\(_2\)CO\(_3\) → H\(^+\) + HCO\(_3^-\). In other words, the loss of extracellular Cl\(^-\) is equivalent to the gain in HCO\(_3^-\) 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 HCO\(_3^-\) ion according to the following reaction: H\(^+\) + HCO\(_3^-\) → H\(_2\)CO\(_3\) → CO\(_2\) + H\(_2\)O. The effect of this reaction is to decrease the non-Na\(^+\) and non-K\(^+\) osmotic in the ICF. The concomitant cellular loss of K\(^+\) will result in the loss of 2 mmol of osmotically active particles (1 mmol of HCO\(_3^-\) and 1 mmol of K\(^+\)) from the ICF per mmol of cellular K\(^+\) lost from the body. The loss of intracellular HCO\(_3^-\) (excreted as CO\(_2\)) will result in a decrease in osmol\(_{\text{ICF}}\) and, therefore, the ratio of Na\(^+\)/K\(^+\) 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 (osmol_{ECF}) because the H+ ions entering the cells are produced along with HCO3− in the ECF by the reaction CO2 + H2O → H2CO3 → H+ + HCO3−.

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 (osmol_{ECF} + osmol_{ICF})/TBW term due to a decrease in the quantity of osmotically active, intracellular non-Na+ and non-K+ osmoses (osmol_{ICF}). 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 (osmol_{ECF} + osmol_{ICF})/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 osmol_{ICF} 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+ osmos (osmol_{ICF}) 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 (osmol_{ECF} + osmol_{ICF})/TBW term due to a decrease in the quantity of osmotically active, extracellular non-Na+ and non-K+ osmos (osmol_{ECF}). 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+ osmoses 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 (osmol_{ICF}) 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+]_{pw} 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+]_{pw} 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+ osmoses 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+ (E_{MB}), and the mass balance of H2O (V_{MB}), 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):

\[
[Na^+]_{pw}^2 = \frac{([Na^+]_{pl} + y_1)TBW_1 + 1.03 \times E_{MB}}{TBW_1 + V_{MB}} - y_2 \tag{3}
\]

where

\[
y = 23.8 + (1.6/100) ([G] - 120)
\]
\[
[E] = [Na^+ + K^+]^2
\]
E_{MB} = (Na^+ + K^+)_{input-output} = mass balance of Na^+ + K^+ in a chosen duration of time.

\[
E_{MB} = (E_{IVF} \times V_{IVF} + E_{oral} \times V_{oral} + E_{tube feed} \times V_{tube feed} + E_{TPN} \times V_{TPN} - E_{urine} \times V_{urine} - E_{GI} \times V_{GI} - E_{sweat} \times V_{sweat}
\]

\[V_{MB} = V_{input} - V_{output} = mass balance of H_2O in a chosen duration of time.

\[V_{MB} = V_{IVF} + V_{oral} + V_{tube feed} + V_{TPN} + V_{oxidation} - V_{urine} - V_{GI} - V_{sweat} - V_{insensible}
\]

\[G = \text{plasma glucose concentration}
\]

\[
[Na^+]_p = \frac{([Na^+]_p + 23.8)TBW_i + 1.03 \times E_{MB} - 23.8}{TBW_i + V_{MB}}
\]

This formula incorporates 1) the known empirical relationship between the [Na^+]_p, Na^+, K^+, and TBW; 2) changes in mass balance of H_2O (V_{MB}); Na^+ + K^+ (E_{MB}); and 3) the effect of hyperglycemia on the [Na^+]_p. This new equation, unlike all previous qualitative and quantitative approaches, can account mathematically for the simultaneous effects of TBW, Na^+, K^+, E_{MB}, V_{MB}, and plasma glucose on the [Na^+]_p. The formula also takes into consideration the fact that plasma is 93% water (2, 9), i.e., 0.93 \times [Na^+]_p = [Na^+]_p. Moreover, by considering the known empirical relationship between the [Na^+]_p, Na^+, K^+, and TBW, the formula accounts for the quantitative and physiological significance of the slope and y-intercept in the Edelman equation. Finally, this simple quantitative formula can be used to explain retrospectively and predict prospectively the generation of the dysnatremias.

The application of Eq. 3 (or Eq. 3A) provides important clinical insights into the pathogenesis of the dysnatremias and clears up common misconceptions. Historically, hypovolemic hyponatremia was considered a disorder of positive water balance rather than a disorder of Na^+ + K^+ imbalance. In contrast to the common misconception that the hyponatremia in patients with volume depletion is generated because of positive water balance due to a decrease in free water excretion, these patients tend to have an E_{MB} (mass balance of Na^+ + K^+) that is negative and is therefore the primary cause of the hyponatremia (21). The V_{MB} (mass balance of H_2O) is also typically negative as expected from the weight loss normally observed in these patients. Therefore, in hypovolemic hyponatremic patients, the negative V_{MB} is contributing to the correction of the hyponatremia but is not of sufficient magnitude to prevent a decrease in the [Na^+]_p. In other words, because patients with hypovolemic hyponatremia typically have a decrease in TBW (rather than a gain in TBW), hypovolemic hyponatremia is therefore a disorder of negative Na^+ and K^+ balance and inadequate negative H_2O balance (rather than a disorder of positive H_2O balance). The negative V_{MB} is inadequate to correct the hyponatremia in these patients due to a defect in urinary water excretion (Table 1).

### Table 1. Pathophysiology of hyponatremia

<table>
<thead>
<tr>
<th>Classification of Hyponatremia</th>
<th>V_{MB}</th>
<th>E_{MB}</th>
<th>Relative Effects of E_{MB} and V_{MB} on [Na^+]_p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic</td>
<td>Negative</td>
<td>Negative</td>
<td>E_{MB} &gt; V_{MB}</td>
</tr>
<tr>
<td>Euvoletic</td>
<td>Positive</td>
<td>Negligible</td>
<td>V_{MB} &gt; E_{MB}</td>
</tr>
<tr>
<td>Hypervolemic</td>
<td>Positive</td>
<td>Positive</td>
<td>E_{MB} &gt; V_{MB}</td>
</tr>
</tbody>
</table>

V_{MB} represents the mass balance of H_2O; E_{MB} represents the mass balance of Na^+ + K^+; [Na^+]_p = plasma water Na^+ concentration.

On the other hand, in euvolemic hyponatremia, the positive V_{MB} is the cause of the decrease in [Na^+]_p, whereas the E_{MB} is negligible in this setting. Similarly, in hypervolemic hyponatremia, the positive V_{MB} is the cause of the hyponatremia. However, in this setting, the positive E_{MB} would tend to raise the [Na^+]_p, but its incremental effect is less than the depressive effect of the positive V_{MB} on the [Na^+]_p.

This type of analysis can also be applied to derive insights into the mechanisms underlying the generation of hyponatremia. In hypovolemic hyponatremia, the negative V_{MB} is the cause of the hyponatremia, whereas the negative E_{MB} in this setting would lower the [Na^+]_p, but its depressive effect is less than the incremental effect of the negative V_{MB} on the [Na^+]_p (Table 2). In these patients, a defect in thirst mechanism or inadequate access to H_2O contributes to the negative V_{MB}. In euvolemic hyponatremia, the negative V_{MB} is also the cause of the hyponatremia, but the E_{MB} is negligible in these patients. Finally, in hypervolemic hyponatremia, it is the positive E_{MB} that is the cause of the hyponatremia (rather than negative V_{MB}); the positive V_{MB} 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 V_{MB} is inadequate to correct the hyponatremia due to a defect in thirst mechanism or inadequate access to H_2O.

### THERAPEUTIC CONSIDERATIONS AND THE ROLE OF Na^+, K^+, AND H_2O IN MODULATING THE [Na^+]_p

Various formulas (Na^+ deficit equation, water deficit equation, Androgue-Madias equation, and Barsoum-Levine equation) have been derived to predict the change in [Na^+]_p after an infusion of Na^+, K^+, and H_2O (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 (\Delta[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 H_2O input that the patient may be receiving in addition to the chosen infusate; 4) any ongoing urinary, gastrointestinal, and cutaneous losses of water and electrolytes; and 5) the known empirical relationship between the [Na^+]_p, Na^+, K^+, and TBW (Eq. 1). Similarly, the water...
deficit equation also has several limitations: 1) it is applicable only for hypernatremia due to pure H2O loss (not hypotonic fluid loss) because the equation assumes that the total body Na+ and K+ remain unchanged with therapy; 2) it assumes that the body is a closed system because it ignores the mass balance of Na+, K+, and H2O; and 3) it ignores the quantitative and physiological significance of the slope and y-intercept in Eq. 1.

Adrogue and Madias (1) proposed a formula for determining the expected ΔNa+ Ip resulting from the retention of 1 liter of a given infusate. There are several limitations inherent in this equation as well. First, when the Androgue-Madias equation is used, the authors suggest that the volume of infusate required to induce a given ΔNa+ Ip can be determined by dividing the ΔNa+ Ip targeted for a given treatment period by the result of this formula (1). This calculation assumes that each additional liter of infusate will induce the same change in the patient’s [Na+] Ip. This assumption is inaccurate because the TBW is not constant. In fact, as the TBW continually changes with therapy, the effect of each additional liter of infusate on the patient’s [Na+] Ip constantly changes as well (25). Second, the formula assumes that the [Na+] Ip is exactly equal to the ratio (Na+ + K+)/TBW. Finally, this equation does not take into consideration any ongoing Na+, K+, and H2O losses, and it does not consider other sources of electrolyte and water input (dietary intake, total parenteral nutrition, and tube feeding) that may also be contributing to the [Na+] Ip (25).

Barsoum and Levine (5) recently proposed a formula that accounts for ongoing renal and extrarenal fluid and electrolyte losses. However, as with the Na+ deficit, water deficit, and Androgue-Madias equations, there are several limitations inherent in this equation as well (25). First, the equation fails to account for other sources of electrolyte and water input (oral intake, total parenteral nutrition, and tube feeding) that may also be contributing to the ΔNa+ Ip. Second, the Barsoum-Levine equation wrongly assumes that [Na+] Ip is exactly equal to the ratio (Na+ + K+)/TBW. Rather, Edelman et al. (14) empirically demonstrated that the [Na+] Ip (as opposed to [Na+] p) 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. 1.

**CONSEQUENCES OF ASSUMING [Na+] Ip IS EQUAL TO (Na+ + K+)/TBW**

Because previous formulas (Na+ deficit equation, water deficit equation, Androgue-Madias equation, and Barsoum-Levine equation) assume that the [Na+] Ip is exactly equal to the ratio (Na+ + K+)/TBW, these formulas also wrongly equate the patient’s Na+ + K+ to the product of the [Na+] Ip and TBW. Implicitly, these formulas assume that the slope in the Edelman equation is equal to one and that the y-intercept is zero (Fig. 1). With the quantitative and physiological significance of the slope and y-intercept in Eq. 1 taken into consideration, the initial Na+ + K+ can be determined as follows (27):

\[
Na_+ + K_+ = \frac{[\text{Na}^+]_{\text{plasma}} + 23.8}{1.03} \times \text{TBW}
\]

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 infusate on the ΔNa+ Ip because the ΔNa+ Ip induced by a given mass balance of Na+, K+, and H2O will vary depending on the initial Na+ + K+ (21, 25, 27, 28). As a result, these formulas may lead to significant errors in the predicted ΔNa+ Ip.

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

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

\[
V_{\text{IVF}} = \frac{[\text{Na}]_1 + 23.8}{[\text{Na}]_2 + 23.8} \times (\text{TBW} \div \frac{V_{\text{output}}}{V_{\text{input}}}) + 0.03(V_{\text{input}} \div V_{\text{output}})
\]

where \( V \) = volume; \( IVF \) = intravenous fluid; \( [\text{Na}]_1 \) = initial plasma sodium concentration; \( [\text{Na}]_2 \) = target plasma sodium concentration; \( E \) = [Na+ + K+]; \( V_{\text{NET}} \) = mass balance of water excluding the volume of IV fluid (\( V_{\text{IVF}} \)) which is being solved for:

\[
V_{\text{NET}} = (V_{\text{oral}} + V_{\text{tube feed}} + V_{\text{TPN}} + V_{\text{oxidation}} - V_{\text{urine}} + V_{\text{GI}} + V_{\text{sweat}} + V_{\text{insensible}})
\]

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

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

\[
V_{\text{IVF}} = \text{intravenous fluid Na}^+ + K^+
\]

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+] Ip; 2) it takes into consideration the fact that plasma is 93% water (2, 9) and that the [Na+] Ipw = 1.11(Na+ + K+)/TBW – 25.6 (Eq. 1); 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 infusate necessary to induce a given Δ[Na+] Ip; 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+] Ip 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 $N_{a_e}$ and $K_{e}$ or intracellular osmotically active, non-$N_{a}$ and non-$K$ 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 $N_{a}$, $K$, and $H_2O$ after administration of a given infusate. Finally, the accuracy of all current formulas is dependent on an accurate measurement 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 $N_{a}$ excretion seen with rapid water expansion in SIADH is associated with a reciprocal depression in urinary $K$ excretion. As a result, the negative $N_{a}$ balance occurring during the rapid increase in TBW is offset by the positive $K$ balance such that the net cumulative loss of $N_{a}$ and $K_e$ 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 $N_{a}$ 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 $\Delta [N_{a}]_{pw}$ in severe symptomatic SIADH in clinical situations where intravenous therapy (hypertonic saline $\pm$ furosemide) is used to increase the $[N_{a}]_{pw}$ more rapidly than water restriction alone. These formulas cannot be used to predict the effect of a given infusate on the $\Delta [N_{a}]_{pw}$ in patients with symptomatic SIADH because they fail to consider the neutral solute balance maintained in these patients (25). Indeed, $N_{a}$ 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 $N_{a}$ and $K$ are excreted in the urine. Correction of hyponatremia in SIADH, therefore, occurs by attaining negative water balance while maintaining neutral $N_{a}$ and $K$ balance. None of the above formulas accounts for the intact $N_{a}$ 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):

$$V_{IVF} = \{TBW_i \times (1 - \frac{[\text{[Na]}]}{23.8}) + V_{\text{input}} - \frac{\{[E]\_\text{input} \times V_{\text{input}} - [E]\_\text{oral} \times V_{\text{oral}} + [E]\_\text{tube feed} \times V_{\text{tube feed}} + [E]\_\text{TPN} \times V_{\text{TPN}}}{[E]_{\text{IVF}}} - [E]_{\text{urine}}\}$$

where $V =$ volume; IVF = intravenous fluid; $[Na]$ = initial plasma sodium concentration; $[Na]_2 = \text{target plasma Na}^+\text{ concentration;}$


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

$V_{\text{oral}} = V_{\text{oral}} + V_{\text{tube feed}} + V_{\text{TPN}} + V_{\text{oxidation}}$

$$[E]_{\text{IVF}} = \text{intravenous fluid [Na}^+ + K\}]$$

$$[E]_{\text{urine}} = \text{urinary [Na}^+ + K\]$$

**SUMMARY**

The empirical relationship between the $[Na]_{pw}$, $Na_e$, $K_e$, 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 ($\phi$) of $Na^+$ salts at physiological concentrations and Gibbs-Donnan and osmotic equilibrium. In addition to $Na_e$, $K_e$, and $Na$, 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 $Na_e$ and $K_e$, $K^+_{pw}$, and the osmotically active non-$Na^-$ and non-$K^-$ 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 $K^+$ 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


