Hypothesis

Are the total exchangeable sodium, total exchangeable potassium and total body water the only determinants of the plasma water sodium concentration?

Minhtri K. Nguyen and Ira Kurtz

Division of Nephrology, David Geffen School of Medicine at UCLA, Los Angeles, USA

Keywords: plasma water sodium concentration; total body water; total exchangeable potassium; total exchangeable sodium

Introduction

The dysnatremias are common electrolyte disorders encountered in hospitalized patients [1]. The pathophysiology and approach to management of these electrolyte disorders have been well characterized. It is well known that the total exchangeable sodium (\(\text{Nae}\)), total exchangeable potassium (\(\text{Ke}\)) and total body water (TBW) are the major determinants of the plasma water sodium concentration (\([\text{Na}^+]_{\text{pw}}\)) [2]. Changes in the mass balance of Na\(^+\), K\(^+\) and water, therefore, determine the quantitative impact on the \([\text{Na}^+]_{\text{pw}}\). Several formulas (sodium deficit equation, water deficit equation, Androgue-Madias equation and Barsoum-Levine equation) have been derived to help predict the changes in plasma Na\(^+\) concentration (\([\text{Na}^+]_{\text{p}}\)) following a therapeutic manoeuvre [3–8]. However, although Edelman et al. [2] demonstrated that the plasma water sodium concentration is equal to 1.11(\(\text{Nae} + \text{Ke}\))/TBW–25.6, the significance of the \(y\)-intercept (–25.6) in this equation has never been evaluated. Indeed, previous analyses of the pathogenesis and treatment of the dysnatremias have failed to consider the quantitative and biological significance of the \(y\)-intercept in this equation. In this article, we show quantitatively the necessity for the \(y\)-intercept and its physiologic and clinical significance. Our analysis demonstrates that there are several determinants of the \(y\)-intercept which independently alter the \([\text{Na}^+]_{\text{pw}}\): the osmotically in active exchangeable Na\(^+\) and K\(^+\), the plasma water \([K^+]_{\text{pw}}\) and the osmotically active non-Na\(^+\) and non-K\(^+\) osmoles. Importantly, changes in these parameters determine the magnitude of hyponatraemia in hyperglycaemia. Although the primary determinants of the \([\text{Na}^+]_{\text{pw}}\) are the \(\text{Nae}\), \(\text{Ke}\) and the TBW, a quantitative understanding of the pathogenesis of the dysnatremias requires that the determinants of the \(y\)-intercept in the Edelman equation are not ignored.

Results

Determination of the physiologic importance of the \(y\)-intercept in Edelman’s equation

Since the body fluid compartments are in osmotic equilibrium: total body water osmolality = plasma water osmolality

Therefore:

\[
\frac{\text{Na}_{\text{osm active}} + \text{K}_{\text{osm active}} + \text{osmol}_{\text{ECF}} + \text{osmol}_{\text{ICF}}}{\text{TBW}} = \frac{\text{Na}_{\text{pw}} + \text{K}_{\text{pw}} + \text{osmol}_{\text{pw}}}{\text{V}_{\text{pw}}}
\]

where: \(\text{Na}_{\text{osm active}} = \) osmotically active Na\(^+\); \(\text{K}_{\text{osm active}} = \) osmotically active K\(^+\); \(\text{osmol}_{\text{ECF}} = \) osmotically active, extracellular non-Na\(^+\) and non-K\(^+\) osmoles; \(\text{osmol}_{\text{ICF}} = \) osmotically active, intracellular non-Na\(^+\) and non-K\(^+\) osmoles; \(\text{Na}_{\text{pw}} = \) plasma water Na\(^+\); \(\text{K}_{\text{pw}} = \) plasma water K\(^+\); \(\text{osmol}_{\text{pw}} = \) osmotically active, plasma water non-Na\(^+\) non-K\(^+\) osmoles; \(\text{V}_{\text{pw}} = \) plasma water volume.

Let \([\text{Na}^+]_{\text{pw}} = \) plasma water Na\(^+\) concentration and \([K^+]_{\text{pw}} = \) plasma water K\(^+\) concentration.

Since: \(\text{Na}_{\text{pw}}/\text{V}_{\text{pw}} = [\text{Na}^+]_{\text{pw}}\) and \(\text{K}_{\text{pw}}/\text{V}_{\text{pw}} = [K^+]_{\text{pw}}\)

\[
\frac{\text{Na}_{\text{osm active}} + \text{K}_{\text{osm active}} + \text{osmol}_{\text{ECF}} + \text{osmol}_{\text{ICF}}}{\text{TBW}} = \frac{[\text{Na}^+]_{\text{pw}} + [K^+]_{\text{pw}} + \text{osmol}_{\text{pw}}}{\text{V}_{\text{pw}}}
\]

Rearranging:

\[
[\text{Na}^+]_{\text{pw}} = \frac{\text{Na}_{\text{osm active}} + \text{K}_{\text{osm active}} + \text{osmol}_{\text{ECF}} + \text{osmol}_{\text{ICF}}}{\text{TBW}} - \frac{[K^+]_{\text{pw}} \cdot \text{osmol}_{\text{pw}}}{\text{V}_{\text{pw}}}
\]
Determinants of the plasma water sodium concentration

It has been shown that exchangeable Na⁺ in bone is bound and is, therefore, osmotically inactive [2,9,10]. More recently, Cameron et al. [11] provided evidence that a major portion of intracellular K⁺ is bound as well and is also osmotically inactive. Hence, not all exchangeable Na⁺ and exchangeable K⁺ are osmotically active. Therefore, in addition to the Naₑ, Kₑ and TBW, each of the four components of the y-intercept must determine the [Na⁺]ₚw in patients with dysnatraemias.

\[
[\text{Na}^+]_{\text{pw}} = \frac{\text{Na}_e + \text{K}_e - (\text{Na}_{\text{oosm inactive}} + \text{K}_{\text{oosm inactive}})}{\text{TBW}} + \frac{\text{osmol}_{\text{ECF}} + \text{osmol}_{\text{ICF}}}{\text{TBW}} - \frac{[K^+]_{\text{pw}} - \text{osmol}_{\text{pw}}}{V_{\text{pw}}}
\]

Therefore, the y-intercept in Edelman’s equation is composed of:

\[
\left[ \frac{(\text{Na}_{\text{oosm inactive}} + \text{K}_{\text{oosm inactive}})}{\text{TBW}} + \frac{\text{osmol}_{\text{ECF}} + \text{osmol}_{\text{ICF}}}{\text{TBW}} - \frac{[K^+]_{\text{pw}} - \text{osmol}_{\text{pw}}}{V_{\text{pw}}} \right]
\]

Discussion

Edelman et al. [2] demonstrated that the [Na⁺]ₚw is equal to 1.11(Naₑ + Kₑ)/TBW−25.6 (Equation 1). Therefore, changes in the [Na⁺]ₚw occur clinically because of alterations in the mass balance of Na⁺ and H₂O. Our analysis, however, reveals that the Naₑ, Kₑ and TBW cannot be the sole determinants of the plasma water sodium concentration. Edelman’s equation delineates the relationship between [Na⁺]ₚw and Naₑ, Kₑ and TBW. However, in this equation, the [Na⁺]ₚw is not equal to the ratio (Naₑ + Kₑ)/TBW as is commonly assumed. Rather, the [Na⁺]ₚw is equal to 1.11(Naₑ + Kₑ)/TBW−25.6 [2]. The necessity for a y-intercept (−25.6) and its physiologic significance has not been recognized previously. In this report, we have shown quantitatively the necessity for a y-intercept in Edelman’s equation and have derived its clinically important components:

\[
[\text{Na}^+]_{\text{pw}} = \frac{\text{Na}_e + \text{K}_e - (\text{Na}_{\text{oosm inactive}} + \text{K}_{\text{oosm inactive}})}{\text{TBW}} + \frac{\text{osmol}_{\text{ECF}} + \text{osmol}_{\text{ICF}}}{\text{TBW}} - \frac{[K^+]_{\text{pw}} - \text{osmol}_{\text{pw}}}{V_{\text{pw}}}
\]

where the y-intercept in Edelman’s equation is represented by four components:

\[
\frac{(\text{Na}_{\text{oosm inactive}} + \text{K}_{\text{oosm inactive}})}{\text{TBW}} + \frac{\text{osmol}_{\text{ECF}} + \text{osmol}_{\text{ICF}}}{\text{TBW}} - \frac{[K^+]_{\text{pw}} - \text{osmol}_{\text{pw}}}{V_{\text{pw}}}
\]

The first parameter in the y-intercept reflects the quantity of osmotically inactive exchangeable Na⁺ and K⁺ per unit of TBW. It has been shown that exchangeable Na⁺ in bone is bound and is, therefore, osmotically inactive [2,9,10]. More recently, Cameron et al. [11] provided evidence that a major portion of intracellular K⁺ is bound as well and is also osmotically inactive. Therefore, both Naₑ and Kₑ in the Edelman equation include osmotically active as well as osmotically inactive components. The osmotically inactive Naₑ and Kₑ are ‘ineffective osmoles’ and therefore do not contribute to the distribution of water between the extracellular and intracellular spaces. Failure to consider the osmotically inactive Naₑ and Kₑ will result in an overestimation of the [Na⁺]ₚw.

\[
\frac{(\text{osmol}_{\text{ECF}} + \text{osmol}_{\text{ICF}})}{\text{TBW}}
\]

The y-intercept is also a reflection of the effect of extracellular and intracellular osmotically active, non-Na⁺ and non-K⁺ osmoles on the [Na⁺]ₚw. Hence, the presence of osmotically active, non-Na⁺ and non-K⁺ osmoles in the intracellular compartment (osmol_{ICF}) results in the osmotic shift of water from the plasma space to the intracellular compartment, thereby increasing the [Na⁺]ₚw. However, it may seem counter-intuitive at first glance that the presence of osmotically active, non-Na⁺ and non-K⁺ osmoles in the extracellular compartment (osmol_{ECF}) will result in an increase in the [Na⁺]ₚw. On the other hand, it is important to realize that the osmotically active, non-Na⁺ and non-K⁺ osmoles in the extracellular compartment (osmol_{ECF}) include osmoles in both the plasma space and the interstitial fluid. The presence of osmotically active, non-Na⁺ and non-K⁺ osmoles in the interstitial fluid, therefore, induce the osmotic shift of water from the plasma space to the interstitial...
because it utilizes [Na\(^+\)]_pw. In contrast, the presence of osmotically active, non-Na\(^+\) and non-K\(^+\) osmoles in the plasma space will lower the [Na\(^+\)]_pw by promoting water shift from the interstitial fluid and intracellular compartment to the plasma space. As only one-fifth of the extracellular fluid is confined to the plasma space [12], it is not surprising that quantitatively the presence of osmotically active, non-Na\(^+\) and non-K\(^+\) osmoles in the extracellular compartment (osmol_{ECF}) will result in a net increment in the [Na\(^+\)]_pw.

\[
[K^+]_{pw}
\]

The [K\(^+\)]_pw also acts as an independent factor contributing to the movement of water between the plasma space, interstitial fluid and intracellular compartment. Clinically, the [K\(^+\)]_pw is maintained within a narrow range by factors which affect transcellular K\(^+\) flux and whole body K\(^+\) mass balance. However, in diseases where the [K\(^+\)]_pw changes significantly, the [Na\(^+\)]_pw must change as predicted by our analysis. Moreover, both the total exchangeable K\(^+\) and the [K\(^+\)]_pw must independently affect the [Na\(^+\)]_pw.

Osmol\(_{pw}/V_{pw}\)

The plasma water osmotically active, non-Na\(^+\) and non-K\(^+\) osmoles contribute to the movement of water between the plasma space, interstitial fluid and intracellular compartment. Specifically, the presence of plasma water osmotically active, non-Na\(^+\) and non-K\(^+\) osmoles (for example, glucose, Ca\(^{2+}\), Mg\(^{2+}\), anions) result in the shift of water from the intracellular compartment and interstitial fluid to the plasma compartment, thereby lowering the [Na\(^+\)]_pw.

Change in the \(y\)-intercept in hyperglycaemia-induced hyponatraemia

An understanding of the parameters that affect the \(y\)-intercept in the Edelman’s equation becomes clinically relevant when analysing the pathogenesis of hyperglycaemia-induced hyponatraemia. Specifically, the commonly used formulae calculating [Na\(^+\)]_p to the sum of Na\(_e\) + K\(_e\) divided by the TBW is not correct because it utilizes [Na\(^+\)]_p rather than [Na\(^-\)]_pw. Moreover, it cannot account for the hyperglycaemia-induced hyponatraemia that is attributable to an osmotic water shift as all three parameters in this formula are unchanged. The failure of this formula to account for hyperglycaemia-induced hyponatraemia attributable to osmotic water shift from the fact that changes in the plasma glucose concentration alter the [Na\(^+\)]_pw because of a corresponding change in the magnitude of several components of the \(y\)-intercept in the Edelman equation. Previously, it has been shown that there is an expected decrease of 1.6 meq/l in the plasma sodium concentration for each 100 mg/dl increment in the plasma glucose concentration assuming no change in the mass balance of Na\(^+\), K\(^+\) and water [13]. It is commonly assumed that the plasma glucose concentration is the sole determinant of hyperglycaemia-induced changes in the [Na\(^+\)]_p. While this concept is not incorrect, it is however incomplete. In fact, the correction factor of 1.6 results from simultaneous changes in three of the four parameters determining the \(y\)-intercept.

Which components of the \(y\)-intercept are altered in a patient with hyperglycaemia? First, hyperglycaemia results in an increase in the ratio (osmol_{ECF} + osmol_{ICF})/TBW. This ratio increases because hyperglycaemia increases the numerator term whereas the denominator remains unchanged. In the hyperglycaemia-induced osmotic shift of water from the intracellular compartment to the extracellular space, the TBW remains constant as the ΔV_{ECF} (change in intracellular volume) is equal to the ΔV_{ICF} (change in extracellular volume). Secondly, the hyperglycaemia-induced osmotic shift of water results in a decrease in the [K\(^+\)]_pw. In the clinical setting, the final [K\(^+\)]_pw will also be affected by the magnitude of subsequent cellular K\(^+\) efflux induced by the decrease in [K\(^+\)]_pw and hyperosmolality [14]. Finally, the plasma water concentration of osmotically active non-Na\(^+\) and non-K\(^+\) osmoles represented by the term osmol_{pw}V_{pw} increases in hyperglycaemia. Therefore, the correction factor of 1.6 results from the net change in all three parameters occurring simultaneously in the setting of hyperglycaemia.

Recently, it has been suggested that the correction factor of 1.6 is not valid at all plasma glucose concentrations [15]. However, these investigators failed to consider the changes in the mass balance of Na\(^+\), K\(^+\) and TBW induced by the hyperglycaemia. Indeed, in the setting of hyperglycaemia, changes in the [Na\(^+\)]_pw result not only from the dilutional effect of hyperglycaemia induced by the translocation of water but also to changes in the mass balance of Na\(^+\), K\(^+\) and TBW. To predict the effect of changes in the Na\(_e\), K\(_e\) and TBW as well as the dilutional effect of hyperglycaemia on the plasma sodium concentration ([Na\(^+\)]_p) attributable to the osmotic shift of water, the correction factor of 1.6 can be incorporated into the Edelman’s equation:

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

Multiplying both sides of the equation by 0.93 to convert [Na\(^+\)]_pw to [Na\(^+\)]_p.

0.93 \times [Na^+]_{pw} = \frac{1.03(Na_e + K_e)}{TBW} - 23.8

Since 0.93 \times [Na^+]_{pw} = [Na^+]_p

\[
[Na^+]_p = \frac{1.03(Na_e + K_e)}{TBW} - 23.8 \tag{3}
\]

In Edelman’s study, the average plasma glucose concentration was 120 mg/dl [2]. Since there is an expected decrease of 1.6 meq/l in the [Na\(^+\)]_p for each 100 mg/dl
increment in the plasma glucose concentration:

\[
\frac{[\text{Na}^+]_\text{p}}{\text{TBW}} = \frac{1.03(N_a + K_e)}{120} - 23.8 - (1.6/100)([\text{glucose}] - 120)
\] (4)

Since hyperglycaemia-induced hyponatraemia can result from changes in the mass balance of Na\(^+\), K\(^+\) and TBW as well as to the dilutional effect of hyperglycaemia induced by the translocation of water, the plasma sodium concentration can be predicted from the following equation: \([\text{Na}^+]_\text{p} = 1.03(N_a + K_e)/\text{TBW} - 23.8 - (1.6/100)([\text{glucose}] - 120)\). Therefore, the y-intercept is not constant in patients with hyperglycaemia and will vary directly with the plasma glucose concentration (Figure 1). This figure illustrates in a graphical manner that for any given \((N_a + K_e)/\text{TBW}\), the \([\text{Na}^+]_\text{p}\) will change depending on the magnitude of the hyperglycaemia-induced shift in the y-intercept.

Since the components of the y-intercept in Edelman’s equation determine the \([\text{Na}^+]_\text{pw}\), it is also important not to ignore the y-intercept in the derivation of formulas used in guiding the treatment of the dysnatraemias. Unfortunately, all currently available formulas (sodium deficit equation, water deficit equation, Androguen–Madias equation and Barsoum–Levine equation) have failed to consider the significance of the y-intercept (\(-25.6\)) by implicitly assuming that the \([\text{Na}^+]_\text{p}\) is equal to the ratio \((N_a + K_e)/\text{TBW}\) [3–8]. Moreover, these formulas cannot account for the net depressive effect of osmotically inactive exchangeable Na\(^+\) and K\(^+\), \([\text{Na}^+]_\text{pw}\) and osmotically active, non-Na\(^+\) and non-K\(^+\) osmoles on the \([\text{Na}^+]_\text{pw}\) (Figure 2). Consequently, by ignoring the y-intercept, these previously published formulas may lead to significant errors in the predicted \(\Delta[\text{Na}^+]_\text{p}\). We have recently corrected this error by taking into consideration the relationship between \([\text{Na}^+]_\text{pw}\), \(N_a\), \(K_e\) and TBW reported by Edelman et al. [2] and have derived the correct formula for clinically predicting the effect of i.v. therapy on the \(\Delta[\text{Na}^+]_\text{p}\) [16].

**Clinical application: practical examples**

**Utility of the y-intercept in the determination of the \(N_a\) and \(K_e\)**. The patient is a 44-year-old woman who presented with symptoms of fatigue, numbness and tingling of the lower extremities, gait instability, decreased appetite, nausea and intermittent vomiting. She was also noted to be increasingly lethargic and confused by her family and was clinically hypovolaemic on exam. Her TBW was estimated to be 25 l using the regression equation reported by Watson et al. [17]. Initial \([\text{Na}^+]_\text{p}\) was 108 meq/l and \([\text{K}^+]_\text{p}\) was 1.8 meq/l. She was thought to have hypovolaemic hyponatraemia and was treated with isotonic saline and KCl. A review of the patient’s fluid input and output indicated that she received 2.9 l of isotonic saline, 190 meq KCl, and 0.8 l of H\(_2\)O. Her urinary output was 2.25 l and the urinary \([\text{Na}^+] + [\text{K}^+]\) was 28 meq/l during this period. Repeat \([\text{Na}^+]_\text{p}\) was 123 meq/l and \([\text{K}^+]_\text{p}\) was 2.9 meq/l. Since previously published formulas assume that the \([\text{Na}^+]_\text{p}\) is exactly equal to the ratio \((N_a + K_e)/\text{TBW}\) [3–8], these formulas also wrongly equate the patient’s \(N_a + K_e\) to the product of the \([\text{Na}^+]_\text{p}\) and TBW. Taking into consideration the physiological significance of the y-intercept, the
\[ \text{Na}^+ + K_e \text{ can be determined using Equation 5:} \]
\[ [\text{Na}^+]_p = \frac{1.03(\text{Na}_e + K_e)}{\text{TBW}} - 23.8 \]

Therefore:
\[ \text{Na}_e + K_e = \frac{([\text{Na}^+]_p + 23.8) \times \text{TBW}}{1.03} \]  
(5)

Consequently, previously published formulas will inaccurately predict the effect of therapy on the \( \Delta[\text{Na}^+]_p \) since the change in the \([\text{Na}^+]_p\) induced by a given mass balance of \( \text{Na}^+ \), \( K^+ \), and water will vary depending on the initial \( \text{Na}_e + K_e \). Applying Equation 5 to the above case, the initial \( \text{Na}_e + K_e \) can be calculated as follows:
\[ \text{Na}_e + K_e = \frac{(108 + 23.8) \times 25}{1.03} \]

\( \text{Na}_e + K_e = 3199 \text{ meq}. \)

Since the patient received 2.9 l of isotonic saline, 190 meq KCl, and 0.8 l of H2O, whereas her urinary output was 2.25 l, with a urinary \([\text{Na}^+ + K^+]\) of 28 meq/l during this period:
\[ \text{Na}_e2 + K_e2 = 3199 + 2.9 \times 154 + 190 - 2.25 \times 28 = 3772.6 \text{ meq} \]
\[ \text{TBW}_2 = 25 + 2.9 + 0.8 - 2.25 = 26.45 \text{ l}. \]

The predicted new \([\text{Na}^+]_p\) can now be determined by applying Equation 3:
\[ [\text{Na}^+]_p = \frac{1.03(\text{Na}_e + K_e)}{\text{TBW}} - 23.8 \]  
(3)
\[ [\text{Na}^+]_p = \frac{1.03(3772.6)}{26.45} - 23.8 = 123 \text{ meq/l} \]

Therefore, Equation 3 correctly predicts the effect of therapy on the \( \Delta[\text{Na}^+]_p \) since it takes into account the significance of the \( y \)-intercept in the determination of the \( \text{Na}_e \) and \( K_e \). In contrast, the Adrogue–Madias equation predicts that the patient’s \([\text{Na}^+]_p\) would have increased from 108 to 120 meq/l if 2.9 l of 0.9% NaCl and 190 meq KCl (amount of i.v. fluid and KCl received by the patient) were administered, whereas the sodium deficit equation predicts that the patient’s \([\text{Na}^+]_p\) would increase from 108 to 133 meq/l. Similarly, the \([\text{Na}^+]_p\) would have increased from 108 to 128 meq/l according to the Barsoum–Levine equation. Therefore, application of the Adrogue–Madias equation, sodium deficit equation and Barsoum–Levine equation would have resulted in an error of 3, 10 and 5 meq/l, respectively.

Importance of the \( y \)-intercept in hyperglycaemia-induced hyponatraemia

The patient is a 56-year-old female who was admitted with diabetic ketoacidosis. Initial laboratory test results were: \([\text{Na}^+]_p = 112 \text{ meq/l}, [K^+]_p = 3.7 \text{ meq/l}, \text{TCO}_2 = 15 \text{ meq/l}, \text{blood glucose} = 850 \text{ mg/dl.} \) Her TBW was estimated to be 31 l using the regression equation reported by Watson et al. [17]. The patient was treated with 4 l of 0.9% saline + 20 meq/l KCl and insulin drip (in 100 ml of 0.9% saline). Other input included 0.7 l of H2O. Her urinary output was 2.8 l, and the urinary \([\text{Na}^+ + K^+]\) was 110 meq/l during this period. Repeat laboratory tests revealed: \([\text{Na}^+]_p = 126 \text{ meq/l} \) and blood glucose 200 mg/dl.

Since hyperglycaemia-induced hyponatraemia results from changes in the mass balance of \( \text{Na}^+ \), \( K^+ \) and TBW as well as to the dilutional effect of hyperglycaemia induced by the translocation of water, Equation 4 is used to determine the initial \( \text{Na}_e + K_e \):
\[ [\text{Na}^+]_p = \frac{1.03(\text{Na}_e + K_e)}{\text{TBW}} - 23.8 \]
\[ - (1.6/100)(\text{[glucose]} - 120) \]  
(4)
\[ 112 = \frac{1.03(\text{Na}_e + K_e)}{31} - 23.8 - (1.6/100)(850 - 120) \]  
(4)

Solving for \( \text{Na}_e + K_e \):
\[ \text{Na}_e + K_e = \frac{(112 + 35.48) \times 31}{1.03} = 4439 \text{ meq} \]

Therefore, \( \text{Na}_e + K_e = 4439 + 174 \times 4 + 154 \times 0.1 - 110 \times 2.8 = 4842.4 \text{ meq} \)
\[ \text{TBW}_2 = 31 + 4 + 0.1 + 0.7 - 2.8 = 33 \text{ l}. \]

The predicted new \([\text{Na}^+]_p\) can now be determined by applying Equation 4 again:
\[ [\text{Na}^+]_p = \frac{1.03(\text{Na}_e + K_e)}{\text{TBW}} - 23.8 \]
\[ - (1.6/100)(\text{[glucose]} - 120) \]  
(4)
\[ [\text{Na}^+]_p = \frac{1.03(4842.4)}{33} - 23.8 - (1.6/100)(200 - 120) \]  
(4)
\[ [\text{Na}^+]_p = 126 \text{ meq/l} \]

This case illustrates the importance of the \( y \)-intercept in evaluating hyperglycaemia-induced hyponatraemia. Hyperglycaemia-induced hyponatraemia results from changes in the mass balance of \( \text{Na}^+ \), \( K^+ \) and TBW (osmotic diuresis, vomiting) as well as the dilutional effect of hyperglycaemia induced by the translocation of water. All these effects are incorporated mathematically in Equation 4. In contrast, both the Adrogue–Madias and Barsoum–Levine equations predict that the patient’s \([\text{Na}^+]_p\) would have increased from 112 to 120 meq/l, whereas the sodium deficit equation predicts an increase in the \([\text{Na}^+]_p\) from 112 to 134 meq/l. Therefore, application of the Adrogue–Madias equation, Barsoum–Levine equation and sodium deficit equation in this case would lead to an error of 6, 6 and 8 meq/l, respectively.

Role of osmotically inactive \( \text{Na}_e \) and \( K_e \) in the determination of the \([\text{Na}^+]_p \)

Although it has been shown that exchangeable \( \text{Na}^+ \) in bone and a major portion of intracellular \( K^+ \) are bound and are osmotically inactive [2,9,10,11], the
significance of osmotically inactive Na\textsubscript{e} and K\textsubscript{e} in the determination of the [Na\textsuperscript{+}]\textsubscript{pw} has not been well appreciated. In SIADH, the quantities of sodium lost and water retained are insufficient to account for the magnitude of the observed reduction in plasma sodium concentration in severely hyponatraemic patients [18,19]. This discrepancy has been attributed to loss or ‘inactivation’ of osmotically active solute. More recently, Heer \textit{et al}. [20] demonstrated positive sodium balance in healthy subjects on a metabolic ward without increases in body weight, expansion of the extracellular space, or plasma sodium concentration. These authors, therefore, suggested that there is osmotic inactivation of exchangeable sodium. Similarly, Titze \textit{et al}. [21] reported sodium accumulation in an osmotically inactive form in human subjects in a terrestrial space station simulation study. These investigators suggested the existence of an osmotically inactive sodium reservoir that exchanges sodium with the extracellular space. Titze \textit{et al}. [22] also showed that salt-sensitive Dahl rats (which developed hypertension if fed a high-sodium diet) were characterized by a reduced osmotically inactive sodium storage capacity in comparison to 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\textsuperscript{+} and K\textsuperscript{+} reservoir, which does not contribute to the distribution of water between the extracellular and intracellular spaces. Hence, previous published formulas which fail to consider the osmotically inactive Na\textsubscript{e} and K\textsubscript{e} (which is reflected by the first parameter in the y-intercept) result in an overestimation of the [Na\textsuperscript{+}]\textsubscript{pw}.

In summary, although Na\textsubscript{e}, K\textsubscript{e}, and TBW are the major determinants of the [Na\textsuperscript{+}]\textsubscript{pw}, we now demonstrate that additional physiologic parameters must also be considered. These parameters are the components of the y-intercept in Edelman’s equation and include the quantity of osmotically inactive exchangeable Na\textsuperscript{+} and K\textsuperscript{+}, the [K\textsuperscript{+}]\textsubscript{pw} and the osmotically active, non-Na\textsuperscript{+} and non-K\textsuperscript{+} osmoles. Since total body water is passively distributed in proportion to osmotic activity, the fact that some of the Na\textsubscript{e} and K\textsubscript{e} are bound and are osmotically inactive must be taken into account in the determination of the [Na\textsuperscript{+}]\textsubscript{pw}. Moreover, we show that the [K\textsuperscript{+}]\textsubscript{pw} and intracellular and extracellular osmotically active, non-Na\textsuperscript{+} and non-K\textsuperscript{+} osmoles also determine the distribution of water between the plasma, interstitial (extracellular) fluid, and intracellular spaces. In patients with hyperglycaemia, the correction factor of 1.6 results from the net change in the [K\textsuperscript{+}]\textsubscript{pw} and concentration of extracellular osmotically active, non-Na\textsuperscript{+} and non-K\textsuperscript{+} osmoles. Since hyperglycaemia also induces changes in the mass balance of Na\textsuperscript{+}, K\textsuperscript{+} and TBW, the plasma sodium concentration can be predicted from the following equation: [Na\textsuperscript{+}]\textsubscript{pw} = 1.03(Na\textsubscript{e} + K\textsubscript{e})/TBW – 23.8 – (1.6/100)([glucose] – 120). By considering all of these factors, clinicians will have a more complete and quantitative understanding of the determinants of the [Na\textsuperscript{+}]\textsubscript{pw} and the pathogenesis and treatment of the dysnatraemias.

Acknowledgements. This work was supported by NIH grants DK-63125, DK-07789, the Max Factor Family Foundation, and the Richard and Hinda Rosenthal Foundation.

References