Hypothesis

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

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Introduction

The dysnatraemias 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 (Na_e), total exchangeable potassium (K_e) and total body water (TBW) are the major determinants of the plasma water sodium concentration ([Na^+]_pw) [2]. Changes in the mass balance of Na^+, K^+ and water, therefore, determine the quantitative impact on the [Na^+]_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 ([Na^+]_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(Na_e + K_e)/TBW–25.6, the significance of the y-intercept (~25.6) in this equation has never been evaluated. Indeed, previous analyses of the pathogenesis of the dysnatraemias 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 [Na^+]_pw: the osmotically inactive exchangeable Na^+ and K^+, the plasma water [K^+] (K^+_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 [Na^+]_pw are the Na_e, K_e and the TBW, a quantitative understanding of the pathogenesis of the dysnatraemias 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:

\[ \frac{Na_{osm\ active} + K_{osm\ active} + osmol_{ECF} + osmol_{ICF}}{TBW} \]

\[ \frac{Na_{pw} + K_{pw} + osmol_{pw}}{V_{pw}} \]

where: Na_{osm\ active} = osmotically active Na^+; K_{osm\ active} = osmotically active K^+; osmol_{ECF} = osmotically active extracellular non-Na^+ and non-K^+ osmoles; osmol_{ICF} = osmotically active intracellular non-Na^+ and non-K^+ osmoles; Na_{pw} = plasma water Na^+; K_{pw} = plasma water K^+; osmol_{pw} = osmotically active plasma water non-Na^+ non-K^+ osmoles; V_{pw} = plasma water volume.

Let [Na^+]_pw = plasma water Na^+ concentration and [K^+]_pw = plasma water K^+ concentration.

Since: Na_{pw}/V_{pw} = [Na^+]_pw and K_{pw}/V_{pw} = [K^+]_pw

\[ \frac{Na_{osm\ active} + K_{osm\ active} + osmol_{ECF} + osmol_{ICF}}{TBW} \]

\[ \frac{[Na^+]_pw + [K^+]_pw + \frac{osmol_{pw}}{V_{pw}}}{TBW} \]

Rearranging:

\[ [Na^+]_pw = \frac{Na_{osm\ active} + K_{osm\ active} + osmol_{ECF} + osmol_{ICF}}{TBW} \]

\[ -[K^+]_pw = \frac{osmol_{pw}}{V_{pw}} \]
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:

Let Na\(_{e}\) = total exchangeable Na\(^{+}\); K\(_{e}\) = total exchangeable K\(^{+}\); Na\(_{osm\ inactive}\) = osmotically inactive Na\(^{+}\); and K\(_{osm\ inactive}\) = osmotically inactive K\(^{+}\).

Since: Na\(_{e}\) = Na\(_{osm\ active}\) + Na\(_{osm\ inactive}\) and K\(_{e}\) = K\(_{osm\ active}\) + K\(_{osm\ inactive}\)

\[
[Na^{+}]_{pw} = \frac{Na_{e} + K_{e} - (Na_{osm\ inactive} + K_{osm\ inactive})}{TBW} + \frac{osmol_{ECF} + osmol_{ICF}}{TBW} - \frac{[K^{+}]_{pw} - osmol_{pw}}{V_{pw}}
\]

\[
[Na^{+}]_{pw} = \frac{Na_{e} + K_{e} - (Na_{osm\ inactive} + K_{osm\ inactive})}{TBW} + \frac{osmol_{ECF} + osmol_{ICF}}{TBW} - \frac{[K^{+}]_{pw} - osmol_{pw}}{V_{pw}}
\]

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

\[
\left\{\frac{(Na_{osm\ inactive} + K_{osm\ inactive})}{TBW} + \frac{osmol_{ECF} + osmol_{ICF}}{TBW} - \frac{[K^{+}]_{pw} - osmol_{pw}}{V_{pw}}\right\}
\]

\[
\left\{\frac{(Na_{osm\ inactive} + K_{osm\ inactive})}{TBW} + \frac{osmol_{ECF} + osmol_{ICF}}{TBW} - \frac{[K^{+}]_{pw} - osmol_{pw}}{V_{pw}}\right\}
\]

Discussion

Edelman et al. [2] demonstrated that the [Na\(^{+}\)]\(_{pw}\) is equal to 1.11(Na\(_{e}\) + K\(_{e}\))/TBW – 25.6 (Equation 1). Therefore, changes in the [Na\(^{+}\)]\(_{pw}\) can occur clinically because of alterations in the mass balance of Na\(^{+}\), K\(^{+}\), and H\(_{2}\)O. Our analysis, however, reveals that the Na\(_{e}\), K\(_{e}\), and TBW cannot be the sole determinants of the plasma water sodium concentration. Edelman’s equation delineates the relationship between [Na\(^{+}\)]\(_{pw}\) and Na\(_{e}\), K\(_{e}\), and TBW. However, in this equation, the [Na\(^{+}\)]\(_{pw}\) is not equal to the ratio (Na\(_{e}\) + K\(_{e}\))/TBW as is commonly assumed. Rather, the [Na\(^{+}\)]\(_{pw}\) is equal to 1.11(Na\(_{e}\) + K\(_{e}\))/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:

\[
[Na^{+}]_{pw} = \frac{Na_{e} + K_{e} - (Na_{osm\ inactive} + K_{osm\ inactive})}{TBW} + \frac{osmol_{ECF} + osmol_{ICF}}{TBW} - \frac{[K^{+}]_{pw} - osmol_{pw}}{V_{pw}}
\]

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

\[
\left\{\frac{(Na_{osm\ inactive} + K_{osm\ inactive})}{TBW} + \frac{osmol_{ECF} + osmol_{ICF}}{TBW} - \frac{[K^{+}]_{pw} - osmol_{pw}}{V_{pw}}\right\}
\]

Therefore, in addition to the Na\(_{e}\), K\(_{e}\) and TBW, each of the four components of the \(y\)-intercept must determine the [Na\(^{+}\)]\(_{pw}\) in patients with dysnatraemias.

\[
\frac{(Na_{osm\ inactive} + K_{osm\ inactive})}{TBW}
\]

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 Na\(_{e}\) and K\(_{e}\) in the Edelman equation include osmotically active as well as osmotically inactive components. The osmotically inactive Na\(_{e}\) and K\(_{e}\) 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 Na\(_{e}\) and K\(_{e}\) will result in an overestimation of the [Na\(^{+}\)]\(_{pw}\).

\[
\frac{(Osmol_{ECF} + osmol_{ICF})}{TBW}
\]

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 extracellular compartment (osmol\(_{ECF}\)) 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...
compartment, thereby increasing the $[Na^+]_{pw}$. 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 (osmolECF) 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 transepidermal $K^+$ 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 formula equating $[Na^+]_p$ 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 results 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 (osmolECF + osmolICF)/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 $\Delta V_{ECF}$ (change in extracellular volume) is equal to the $\Delta V_{ICF}$ (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:

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

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

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

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:

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

(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: 

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

Therefore, the \(y\)-intercept is not constant in 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 \((\text{Na}_e + \text{K}_e)/\text{TBW}\), the \([\text{Na}^+\]_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}^+\]_p\), it is also important not to ignore the \(y\)-intercept in the derivation of formulas used in guiding the treatment of dysnatraemias. Unfortunately, all currently available formulas (sodium deficit equation, water deficit equation, Androgue-Madias equation and Barsoum-Levine equation) have failed to consider the significance of this \(y\)-intercept (-25.6) by implicitly assuming that the \([\text{Na}^+\]_p\) is equal to the ratio \((\text{Na}_e + \text{K}_e)/\text{TBW}\) [3-8]. Moreover, these formulas cannot account for the net depressive effect of osmotically inactive exchangeable Na\(^+\) and K\(^+\), \([\text{Na}^+\]_p\) and osmotically active, non-Na\(^+\) and non-K\(^+\) osmoles on the \([\text{Na}^+\]_p\) (Figure 2). Consequently, by ignoring the \(y\)-intercept, these previously published formulas may lead to significant errors in the predicted \(\Delta[\text{Na}^+]_p\). We have recently corrected this error by taking into consideration the relationship between \([\text{Na}^+\]_p\), \(\text{Na}_e\), \(\text{K}_e\) 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 \(\Delta[\text{Na}^+]_p\) [16].

**Clinical application: practical examples**

Utility of the \(y\)-intercept in the determination of the \(\text{Na}_e\) and \(\text{K}_e\). 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}^+\]_p\) was 108 meq/l and \([\text{K}^+\]_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}^+\]_p\) was 123 meq/l and \([\text{K}^+\]_p\) was 2.9 meq/l. Since previously published formulas assume that the \([\text{Na}^+\]_p\) is exactly equal to the ratio \((\text{Na}_e + \text{K}_e)/\text{TBW}\) [3-8], these formulas also wrongly equate the patient’s \(\text{Na}_e + \text{K}_e\) to the product of the \([\text{Na}^+\]_p\) and TBW. Taking into consideration the physiological significance of the \(y\)-intercept, the

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**Fig. 1.** Dependence of the \(y\)-intercept of the Edelman equation on the plasma glucose concentration. As the plasma glucose concentration increases, the \(y\)-intercept in the Edelman equation increases in a predictable manner resulting in a decrease in the \([\text{Na}^+\]_p\) as calculated according to the following formula (y-axis): 

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

**Fig. 2.** Comparison of the \([\text{Na}^+\]_p\) (meq/l) calculated according to \([\text{Na}^+\]_p\) = (\(\text{Na}_e + \text{K}_e\))/\text{TBW\} (black line) vs \([\text{Na}^+\]_p\) = 1.03(\(\text{Na}_e + \text{K}_e\))/\text{TBW\} - 23.8 (red line). Note that the \(y\)-intercept is 23.8 at a plasma glucose of 120 mg/dl. At any given \((\text{Na}_e + \text{K}_e)/\text{TBW}\), the components of the \(y\)-intercept, which include osmotically inactive exchangeable Na\(^+\) and K\(^+\), plasma [K\(^+\)], and osmotically active non-Na\(^+\) and non-K\(^+\) osmoles, result in a net depressive effect on the \([\text{Na}^+\]_p\).
Na\(_e\) + K\(_e\) can be determined using Equation 5:
\[
[\text{Na}^+]_p = \frac{1.03(\text{Na}_e + \text{K}_e)}{\text{TBW}} - 23.8
\]

Therefore:
\[
\text{Na}_e + \text{K}_e = \frac{([\text{Na}^+]_p + 23.8) \times \text{TBW}}{1.03}
\] (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 \(\text{Na}^+\), \(\text{K}^+\), and water will vary depending on the initial \(\text{Na}_e + \text{K}_e\). Applying Equation 5 to the above case, the initial \(\text{Na}_e + \text{K}_e\) can be calculated as follows:
\[
\text{Na}_e + \text{K}_e = \frac{(108 + 23.8) \times 25}{1.03}
\]

Na\(_e\) + K\(_e\) = 3199 meq.

Since the patient received 2.9 l of isotonic saline, 190 meq KCl, and 0.8 l of H\(_2\)O, whereas her urinary output was 2.25 l, with a urinary \([\text{Na}^+ + \text{K}^+]\) of 28 meq/l during this period:
\[
\text{Na}_e + \text{K}_e = 3199 + 2.9 \times 154 + 190 - (2.25 \times 28) = 3772.6 \text{ meq}
\]
\[
\text{TBW}_2 = 25 + 2.9 + 0.8 - 2.25 = 26.45 \text{ l}
\]
The predicted new \([\text{Na}^+]_p\) can now be determined by applying Equation 3:
\[
[\text{Na}^+]_p = \frac{1.03(\text{Na}_e + \text{K}_e)}{\text{TBW}} - 23.8
\]
\[
[\text{Na}^+]_p = \frac{1.03(3772.6)}{26.45} - 23.8 = 123 \text{ meq/l}
\] (3)

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 \(\text{K}_e\). 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: \([\text{Na}^+]_p = 112 \text{ meq/l}, [\text{K}^+]_p = 3.7 \text{ meq/l}, \text{TCO}_2 = 15 \text{ meq/l}, \text{blood glucose} = 850 \text{ mg/dl}\). 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 H\(_2\)O. Her urinary output was 2.8 l, and the urinary \([\text{Na}^+ + \text{K}^+]\) 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 \(\text{Na}^+\), \(\text{K}^+\) 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 \(\text{Na}_e + \text{K}_e\):
\[
[\text{Na}^+]_p = \frac{1.03(\text{Na}_e + \text{K}_e)}{\text{TBW}} - 23.8
\]
\[
- (1.6/100)(\text{[glucose]} - 120)
\]
\[
112 = \frac{1.03(\text{Na}_e + \text{K}_e)}{31} - 23.8 - (1.6/100)(850 - 120)
\] (4)

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

Therefore, \(\text{Na}_e + \text{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:
\[
[\text{Na}^+]_p = \frac{1.03(\text{Na}_e + \text{K}_e)}{\text{TBW}} - 23.8
\]
\[
- (1.6/100)(\text{[glucose]} - 120)
\]
\[
\text{[Na}^+]_p = \frac{1.03(4842.4)}{33} - 23.8 - (1.6/100)(200 - 120)
\] (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 \(\text{Na}^+, \text{K}^+\), 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 \(\text{K}_e\) 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 \(\text{K}^+\) are bound and are osmotically inactive [2,9,10,11], the
significance of osmotically inactive $\text{Na}_e$ and $\text{K}_e$ in the determination of the $[\text{Na}^+]_{\text{pw}}$ 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 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 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 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 $\text{Na}^+$ and $\text{K}^+$ 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 $\text{Na}_e$ and $\text{K}_e$ (which is reflected by the first parameter in the $y$-intercept) result in an overestimation of the $[\text{Na}^+]_{\text{pw}}$.

In summary, although $\text{Na}_e$, $\text{K}_e$, and TBW are the major determinants of the $[\text{Na}^+]_{\text{pw}}$, 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 $\text{Na}^+$ and $\text{K}^+$, the $[\text{K}^+]_{\text{pw}}$ and the osmotically active, non-$\text{Na}^+$ and non-$\text{K}^+$ osmole.

Determinants of the plasma water sodium concentration $[\text{Na}^+]_{\text{pw}}$, and the pathogenesis and treatment of the dysnatremias.

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