A new formula for predicting alterations in plasma sodium concentration in peritoneal dialysis

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Nguyen, Minhtri K., and Ira Kurtz. A new formula for predicting alterations in plasma sodium concentration in peritoneal dialysis.* Am J Physiol Renal Physiol 288: F1113–F1117, 2005; doi:10.1152/ajprenal.00387.2004.—Alterations in the plasma water sodium concentration ([Na+]pw) result from changes in the total exchangeable sodium (Nae), total exchangeable potassium (Ke), and total body water (TBW). The empirical relationship between the [Na+]pw and Nae, Ke, and TBW was originally demonstrated (Edelman IS, Leibman J, O’Meara MP, and Birkenfeld LW. J Clin Invest 37: 1236–1256, 1958), where [Na+]pw = 1.11(Nae + Ke) / TBW – 25.6 (Eq. 1). Based on Eq. 1, alterations in the [Na+]pw can be predicted by considering changes in the mass balance of Na+, K+, and H2O. In accounting for the mass balance of Na+, K+, and H2O in patients on peritoneal dialysis, considerations must also be taken to determine the modulating effect of dialysate clearance of Na+ and K+ and fluid changes resulting from this therapeutic modality on the [Na+]pw. In this article, we derive a new formula for predicting alterations in the plasma Na+ concentration ([Na+]p) in patients on peritoneal dialysis, taking into consideration the empirical relationship between the [Na+]pw and Nae, Ke, and TBW (Eq. 1) as well as changes in mass balance of Na+ + K+ and H2O.

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

Since the normal plasma water content is 93 ml/100 ml plasma (2, 8), multiplying both sides of the equation by 0.93 converts [Na+]pw to [Na+]p.

\[
0.93 \times [\text{Na}^+]_{\text{pw}} = 1.03 \frac{(\text{Nae} + \text{Ke})}{\text{TBW}} - 23.8 \tag{2}
\]

Since 0.93 \times [Na+]pw = [Na+]p.

\[
[\text{Na}^+]_{\text{p1}} = 1.03 \frac{(\text{Nae1} + \text{Ke1})}{\text{TBW1}} - 23.8 \tag{2A}
\]

where [Na+]p1 = initial plasma Na+ concentration, and Nae1, Ke1, and TBW1 represent the initial Nae, Ke, and TBW, respectively.

A change in (Nae1 + Ke1) is caused by an alteration in the mass balance of Na+ + K+ where

\[ E_{MB} = \text{mass balance of Na}^+ + \text{K}^+ \]

Similarly, a change in TBW1 is caused by an alteration in the mass balance of H2O where

\[ V_{MB} = \text{mass balance of water} \]

In accounting for the mass balance of Na+, K+, and H2O in patients on PD, considerations must be taken to determine the modulating effect of Na+, K+, and H2O changes resulting from PD on the [Na+]p. The alterations in Na+, K+, and H2O resulting from this dialytic modality can be determined by considering the net change in the quantities of Na+, K+, and H2O of the infused peritoneal dialysate and the peritoneal dialysate effluent.

Therefore

\[
\text{PD changes in quantity of Na}^+ + \text{K}^+ = [E_{\text{infused dialysate}} \times V_{\text{infused dialysate}}] - [E_{\text{dialysate effluent}} \times V_{\text{dialysate effluent}}] \tag{3}
\]

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PD changes in volume of H2O = Vinfused dialysate − Vdialysate effluent

\[ [E] = [Na^+ + K^+]; \text{V} = \text{volume} \]

To account for the dialytic and nondialytic changes in the mass balance of Na\(^+\) + K\(^+\) (EMB) and H2O (VMB)

\[ E_{MB} = [E]_{input} \times V_{input} - [E]_{output} \times V_{output} + ([E]_{infused dialysate} \times V_{infused dialysate} - [E]_{dialysate effluent} \times V_{dialysate effluent}) \]

\[ V_{MB} = V_{input} - V_{output} + (V_{infused dialysate} - V_{dialysate effluent}) \]

Where

\[ [E]_{input} \times V_{input} - [E]_{output} \times V_{output} = \text{non-PD changes in quantity of Na}^+ + K^+ \]

\[ V_{input} - V_{output} = \text{non-PD changes in volume of H}_2\text{O} \]

According to Eq. 2

\[ [Na^+]_{p2} = 1.03 \frac{(Na_{e2} + K_{e2})}{TBW_2} - 23.8 \]

\[ (Na_{e1} + K_{e1}) = \frac{([Na^+]_{p1} + 23.8)TBW_1}{0.03} \]

Substituting Eq. 2C for (Na_{e1} + K_{e1}) in Eq. 7

\[ [Na^+]_{p2} = 1.03 \left[ \frac{([Na^+]_{p1} + 23.8)TBW_1}{0.03} + E_{MB} \right] / (TBW_1 + V_{MB}) - 23.8 \]

Simplifying

\[ [Na^+]_{p2} = \frac{([Na^+]_{p1} + 23.8)TBW_1 + 1.03 \times E_{MB}}{TBW_1 + V_{MB}} - 23.8 \]

Where

\[ [E] = [Na^+ + K^+]; \text{V} = \text{volume} \]

\[ E_{MB} = \text{mass balance of Na}^+ + K^+ = [E]_{input} \times V_{input} - [E]_{output} \times V_{output} + ([E]_{infused dialysate} \times V_{infused dialysate} - [E]_{dialysate effluent} \times V_{dialysate effluent}) \]

\[ V_{MB} = \text{mass balance of H}_2\text{O} = V_{input} - V_{output} + (V_{infused dialysate} - V_{dialysate effluent}) \]

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

Therefore, to account for the fact that 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 (16), Eq. 8 must be generalized as follows:

\[ [Na^+]_{p2} = \frac{([Na^+]_{p1} + y)TBW_1 + 1.03 \times E_{MB}}{TBW_1 + V_{MB}} - y \]

Where

\[ y = 23.8 + (1.6/100)([\text{glucose}]_p - 120) \]

**DISCUSSION**

Alterations in the Na\(_e\), K\(_e\), and TBW lead to changes in the [Na\(^+\)]\(_p\) (11). Edelman et al. (11) showed empirically that the [Na\(^+\)]\(_pw\) is related to the Na\(_e\), K\(_e\), and TBW by the following equation: [Na\(^+\)]\(_pw\) = 1.11(Na\(_e\) + K\(_e\))/TBW - 25.6 (Eq. 1). This study was the first to demonstrate that the Na\(_e\), K\(_e\), and TBW are the major determinants of the [Na\(^+\)]\(_pw\). According to Eq. 1, one can therefore predict alterations in the [Na\(^+\)]\(_pw\) by accounting for the mass balance of Na\(^+\), K\(^+\), and H\(_2\)O. In patients on PD, the mass balance of Na\(^+\), K\(^+\), and H\(_2\)O will be affected by the diffusive and convective transport of Na\(^+\) and K\(^+\) as well as the ultrafiltration of H\(_2\)O. Diffusive transport results from the passive diffusion of Na\(^+\) and K\(^+\) down their concentration gradient from the plasma into the dialysate or vice versa. In addition, the convective transport of Na\(^+\) and K\(^+\) across the peritoneal membrane occurs via the solvent drag effect of Na\(^+\), K\(^+\), and H\(_2\)O. Moreover, changes in TBW also occur during PD via the process of ultrafiltration.

In this article, we have derived a new formula for predicting alterations in the [Na\(^+\)]\(_p\) in patients on PD. This new formula takes into consideration the fact that changes in the [Na\(^+\)]\(_p\) result from alterations in the Na\(_e\), K\(_e\), and TBW by accounting for the mass balance of Na\(^+\), K\(^+\), and H\(_2\)O. In addition to considering changes in the non-PD mass balance of Na\(^+\), K\(^+\), and H\(_2\)O, alterations in the mass balance of Na\(^+\), K\(^+\), and H\(_2\)O attributed to PD are accounted for in Eq. 8 by determining the net change in the quantities of Na\(^+\), K\(^+\), and H\(_2\)O of the infused peritoneal dialysate and the peritoneal dialysate effluent (Eqs. 3 and 4). Importantly, Eqs. 3 and 4 take into
consideration the net change in the quantities of Na\(^+\), K\(^+\), and H\(_2\)O resulting from the diffusive and convective transport of Na\(^+\) and K\(^+\) as well as the ultrafiltration of H\(_2\)O in PD. Moreover, it is well known that only 93% of plasma is normally composed of H\(_2\)O, whereas fat and proteins account for the remaining 7% (2, 8). Accordingly, Eq. 8 incorporates the fact that plasma is 93% water in its derivation.

There is also abundant evidence that changes in K\(^+\) balance alter the [Na\(^+\)]\(_p\) (6, 11–13, 18, 24–26, 34). Indeed, Zevallas et al. (34) and Cherney et al. (6) reported that intracellular K\(^+\) loss in patients on PD can result in the development of hyponatremia by inducing the shift of water out of cells. These authors suggested that K\(^+\) must be lost from the body along with an intracellular anion or be accompanied by a gain of Na\(^+\) or H\(^+\) in the intracellular compartment. The intracellular anions lost are organic phosphates derived primarily from macromolecules such as RNA, which are subsequently excreted along with K\(^+\) during PD. Accordingly, Eq. 8 accounts for the effect of K\(^+\) on the [Na\(^+\)]\(_p\) by considering the mass balance of K\(^+\). Furthermore, Eq. 8 is derived based on the known empirical relationship between the [Na\(^+\)]\(_p\), Na\(_e\), Ke, and TBW reported by Edelman et al. (11): [Na\(^+\)]\(_p\) = 1.11(Na\(_e\) + Ke)/TBW – 25.6. Unlike previous analyses of the pathogenesis and treatment of the dysnatremias (1, 3, 7, 14, 20, 27–29, 31), Eq. 8 accounts for the physiological and quantitative significance of the slope (1.11) and \(y\)-intercept (−25.6) in Edelman’s equation.

Various analyses of the pathogenesis and treatment of the dysnatremias have failed to consider the quantitative and physiological significance of the slope and \(y\)-intercept in Edelman’s equation (1, 3, 7, 14, 20, 27–29, 31). Indeed, these analyses have failed to consider the physiological significance of the slope (1.11) and \(y\)-intercept (−25.6) by implicitly assuming that the [Na\(^+\)]\(_p\) is exactly equal to the ratio (Na\(_e\) + Ke)/TBW (1, 3, 7, 14, 20, 27–29, 31). By assuming that the [Na\(^+\)]\(_p\) is exactly equal to the ratio (Na\(_e\) + Ke)/TBW, these analyses also erroneously equate the patient’s Na\(_e\) + Ke to the product of the [Na\(^+\)]\(_p\) and TBW. Recently, new insights into the pathophysiology and treatment of the dysnatremias have highlighted the quantitative and physiological significance of the slope and \(y\)-intercept in the Edelman equation (17, 21–26). We have demonstrated that the empirically determined slope of 1.11 in the Edelman equation (11) can be theoretically predicted by considering the combined effect of the osmotic coefficient of Na\(^+\) salts at physiological concentrations and Gibbs-Donnan equilibrium (24, 25). The ionic interactions between Na\(^+\) and its associated anions (as reflected by the osmotic coefficient of Na\(^+\) salts) have a modulating effect on the [Na\(^+\)]\(_p\). Moreover, our mathematical analysis demonstrated that Gibbs-Donnan equilibrium has an incremental effect on the [Na\(^+\)]\(_p\). Because the presence of negatively charged, impermeant proteins in the plasma space alters the distribution of Na\(^+\) and Cl\(^-\) ions between the plasma and interstitial fluid to preserve electro-neutrality, the Gibbs-Donnan effect raises the [Na\(^+\)]\(_p\) at any given quantity of (Na\(_e\) + Ke)/TBW (24, 25).

There are several determinants of the \(y\)-intercept in the Edelman equation which independently alter the [Na\(^+\)]\(_p\): osmotically inactive exchangeable Na\(_e\) and K\(^+\), plasma water [K\(^+\)], and osmotically active non-Na\(_e\) and non-K\(^+\) osmoles (21, 23–26). There is convincing evidence for the existence of an osmotically inactive Na\(_e\) and K\(^+\) reservoir (5, 9–11, 15, 30, 32, 33). These osmotically inactive Na\(_e\) and K\(_e\) are ineffective osmoles, and they do not contribute to the distribution of water between the extracellular and intracellular compartments. Because the Na\(_e\) and K\(_e\) in the Edelman equation include osmotically active as well as osmotically inactive components, 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 (23–25). Moreover, the other components of the \(y\)-intercept reflect the fact that non-Na\(^+\) osmoles are also involved in the distribution of water between the body fluid compartments (23–25). Therefore, the components of the \(y\)-intercept reflect the role of osmotic equilibrium in the modulation of the [Na\(^+\)]\(_p\).

Taking into consideration the quantitative and physiological significance of the slope and \(y\)-intercept in the Edelman equation, we have demonstrated that the initial Na\(_e\) + K\(_e\) can be determined as follows (17, 21, 23–25):

\[
\text{Na}_e + \text{K}_e = \frac{([\text{Na}^+]_p + 23.8) \times \text{TBW}}{1.03}
\]

Accordingly, Eq. 2C is incorporated in the derivation of Eq. 8. In addition, by utilizing the complete Edelman equation in its derivation, Eq. 8 takes into consideration the modulating effect of Gibbs-Donnan and osmotic equilibrium on the [Na\(^+\)]\(_p\).

As the slope and \(y\)-intercept in the Edelman equation have several determinants, alterations in these parameters induced by PD are expected to result in changes in the slope and \(y\)-intercept in Eq. 1. Since the slope of Eq. 1 is determined by the combined effect of the osmotic coefficient of Na\(^+\) salts at physiological concentrations and Gibbs-Donnan equilibrium (24, 25), hypoalbuminemia resulting from dialysate protein loss and malnutrition would be expected to change the slope of Eq. 1 by altering Gibbs-Donnan equilibrium. The magnitude of change in the slope of Eq. 1 induced by hypoalbuminemia is unknown at the present time and is the subject of current investigation. Similarly, alterations in the parameters comprising the \(y\)-intercept would lead to a change in its magnitude. As patients undergoing PD are exposed to a continuous infusion of glucose via their peritoneal cavity, poor glycemic control in diabetic patients on PD would result in an alteration in the magnitude of the \(y\)-intercept. Indeed, we have previously demonstrated that 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 (17, 23–25). Consequently, a modified \(y\)-intercept must be utilized in the setting of hyperglycemia-induced hyponatremia because hyperglycemia will lead to changes in several components of the \(y\)-intercept (17, 23–25).

Poor glycemic control is common in diabetic patients on PD due to dialysate glucose absorption (19). In addition to the alterations in Na\(_e\), Ke, and TBW, changes in the [Na\(^+\)]\(_p\) in these patients also reflect the dilutional effect of plasma glucose on the [Na\(^+\)]\(_p\). It is well known that 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 resulting from the osmotic shift of water between the intracellular fluid compartment and the extracellular fluid compartment (16). This dilutional effect of plasma glucose on the [Na\(^+\)]\(_p\) is reflected by a change in the magnitude of the \(y\)-intercept. Indeed, we have demonstrated that the magnitude of the \(y\)-intercept will vary
directly with the plasma glucose concentration as a result of changes in several components of the y-intercept (17, 23–25). Our analysis also indicated that the following formula can be used to predict the effect of changes in the Na\textsubscript{e}, K\textsubscript{e}, and TBW as well as the dilutional effect of hyperglycemia on the [Na\textsuperscript{+}]\textsubscript{p} attributable to the osmotic shift of water where [Na\textsuperscript{+}]\textsubscript{p} = 1.03(Na\textsubscript{e} + K\textsubscript{e})/TBW - 23.8 - (1.6/100)(glucose\textsubscript{p} - 120) (17, 23–25). Thus, to account for the dilutional effect of hyperglycemia on the [Na\textsuperscript{+}]\textsubscript{p}, Eq. 8 must be generalized as follows:

\[
[Na^{+}]_p = \frac{([Na^{+}]_p + y)TBW + 1.03 \times E_{MB}}{TBW + V_{MB}} - y^2
\]

where

\[
y = 23.8 + (1.6/100)([glucose]_p - 120)
\]

This modification of Eq. 8 simply reflects the fact that the y-intercept varies in a predictable fashion with the [glucose]\textsubscript{p} and needs to be modified in patients where the [glucose]\textsubscript{p} differs significantly from 120 mg/dl.

**CLINICAL APPLICATION**

Equation 8 can be utilized to assess the mechanisms underlying changes in the [Na\textsuperscript{+}]\textsubscript{p} in patients on PD. The utility of Eq. 8 can be illustrated in a patient on PD who presented with acute pancreatitis. The patient is a 46-yr-old anuric male with a dry weight of 66.5 kg. Initial laboratory studies revealed a [Na\textsuperscript{+}]\textsubscript{p} = 130 mmol/l, [K\textsuperscript{+}]\textsubscript{p} = 4 mmol/l, [glucose]\textsubscript{p} = 110 mg/dl. The patient was made NPO, and half-isotonic saline (77 mmol/l) was administered at a rate of 100 ml/h. Twenty-four mg/dl. The patient was made NPO, and half-isotonic saline (77 mmol/l) was administered at a rate of 100 ml/h. Twenty-four hours later, laboratory evaluation revealed a [Na\textsuperscript{+}]\textsubscript{p} = 128 mmol/l, [K\textsuperscript{+}]\textsubscript{p} = 3.5 mmol/l, and [glucose]\textsubscript{p} = 125 mg/dl. Analysis of the peritoneal dialysate revealed an infusate [Na\textsuperscript{+} + K\textsuperscript{+}] of 132 mmol/l, an infusate volume of 10 liters, an effluent [Na\textsuperscript{+} + K\textsuperscript{+}] of 125 mmol/l, and an effluent volume of 11.2 liters, respectively.

The modulating effect of Na\textsuperscript{+}, K\textsuperscript{+}, and H\textsubscript{2}O changes resulting from PD on the [Na\textsuperscript{+}]\textsubscript{p} can be determined by considering the effect of a net change in the quantities of Na\textsuperscript{+}, K\textsuperscript{+}, and H\textsubscript{2}O of the infused peritoneal dialysate and the peritoneal dialysate effluent on the [Na\textsuperscript{+}]\textsubscript{p}. If one were to assume that there is no input (i.e., half-isotonic saline infusion), the dialytic changes in Na\textsuperscript{+}, K\textsuperscript{+}, and H\textsubscript{2}O would be expected to increase the [Na\textsuperscript{+}]\textsubscript{p} from 130 to 132.6 mmol/l according to Eq. 8. On the other hand, the effect of half-isotonic saline administration alone would be expected to lower the [Na\textsuperscript{+}]\textsubscript{p} from 130 to 125.8 mmol/l. Finally, if both dialytic and nondialytic changes in the mass balance of Na\textsuperscript{+}, K\textsuperscript{+}, and H\textsubscript{2}O were considered, calculation based on Eq. 8 would predict that the [Na\textsuperscript{+}]\textsubscript{p} would decrease from 130 to 128 mmol/l. Therefore, the utility of Eq. 8 provides important insights into the mechanism of the generation of the hyponatremia in this patient. The dialytic changes in Na\textsuperscript{+}, K\textsuperscript{+}, and H\textsubscript{2}O balance actually contribute to the correction of the hyponatremia but is not of sufficient magnitude to prevent the decrease in the [Na\textsuperscript{+}]\textsubscript{p} induced by the administration of half-isotonic saline.

In summary, in patients on PD, alterations in the [Na\textsuperscript{+}]\textsubscript{p} occur as a result of the dialytic and nondialytic changes in the mass balance of Na\textsuperscript{+}, K\textsuperscript{+}, and H\textsubscript{2}O as well as the dilutional effect of plasma glucose on the [Na\textsuperscript{+}]\textsubscript{p}. To date, there has not been any quantitative approach that can incorporate mathematically in a single equation the known factors that account quantitatively for changes in the [Na\textsuperscript{+}]\textsubscript{p} in patients on PD. In this article, we have derived a new formula for predicting alterations in the [Na\textsuperscript{+}]\textsubscript{p} in patients on PD. This formula incorporates 1) the known empirical relationship between the [Na\textsuperscript{+}]\textsubscript{pw}, Na\textsubscript{e}, K\textsubscript{e}, and TBW; 2) dialytic and nondialytic changes in the mass balance of Na\textsuperscript{+} + K\textsuperscript{+} (E\textsubscript{MB}) and H\textsubscript{2}O (V\textsubscript{MB}); and 3) the effect of hyperglycemia on the [Na\textsuperscript{+}]\textsubscript{p}. This new equation, unlike previous qualitative and quantitative approaches (1, 3, 7, 14, 20, 27–29, 31), can account mathematically for the simultaneous effects of Na\textsubscript{e}, K\textsubscript{e}, TBW, E\textsubscript{MB}, V\textsubscript{MB}, and plasma glucose on the [Na\textsuperscript{+}]\textsubscript{p}. The formula also takes into consideration the fact that plasma is 93% water (2, 8). In addition, by considering the known empirical relationship between the [Na\textsuperscript{+}]\textsubscript{pw}, Na\textsubscript{e}, K\textsubscript{e}, and TBW (11), the formula accounts for the quantitative and physiological significance of the slope and y-intercept in the Edelman equation. Moreover, this formula can be used to explain retrospectively and predict prospectively the changes in the [Na\textsuperscript{+}]\textsubscript{p} in patients on PD. Finally, this new formula can be generalized to quantitatively predict alterations in the [Na\textsuperscript{+}]\textsubscript{p} in patients on hemodialysis as well.

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