Correction of hypervolaemic hypernatraemia by inducing negative Na\(^+\) and K\(^+\) balance in excess of negative water balance: a new quantitative approach

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Abstract

**Background.** Hypervolaemic hypernatremia is caused by an increase in total exchangeable Na\(^+\) and K\(^+\) in excess of an increment in total body H\(_2\)O (TBW). Unlike patients with hypovolemic or euvolemic hypertremia, treatment needs to be targeted at correcting not only the elevated plasma Na\(^+\) concentration, but also there is an additional requirement to achieve negative H\(_2\)O balance to correct the increment in TBW.

**Methods.** Correction of hypervolaemic hypernatremia can be attained by ensuring that the negative Na\(^+\) and K\(^+\) balance exceeds the negative H\(_2\)O balance. These seemingly conflicting therapeutic goals are typically approached by administering intravenous 5% Dextrose (IV D5W) and furosemide.

**Results.** Currently, there is no quantitative approach to predicting the volume of IV D5W (\(V_{\text{IVF}}\)) that needs to be administered that satisfies these requirements. Therefore, based on the principle of mass balance and the empirical relationship between exchangeable Na\(^+\), K\(^+\), TBW, and the plasma Na\(^+\) concentration, we have derived a new equation which calculates the volume of IV D5W (\(V_{\text{IVF}}\)) needed to lower the plasma Na\(^+\) concentration (\([\text{Na}\(^+\)]_{\text{p1}}\)) to a targeted level (\([\text{Na}\(^+\)]_{\text{p2}}\)) by achieving the desired amount of negative H\(_2\)O balance (\(V_{\text{MB}}\)).

\[
V_{\text{IVF}} = \left(\left([\text{Na}\(^+\)]_{\text{p1}} + 23.8\right) - \left([\text{Na}\(^+\)]_{\text{p2}} + 23.8\right)\right) - V_{\text{MB}} + 1.03 \left(E_{\text{input}} \times V_{\text{input}} - E_{\text{output}} \times V_{\text{output}} - E_{\text{ urine}} \times \left(V_{\text{input}} - V_{\text{output}} - V_{\text{MB}}\right)\right) / 1.03 \times E_{\text{ urine}}\]

where \([\text{Na}\(^+\)]_{\text{p2}}\) and input and output refer to non-infusate and non-renal input and output respectively.

**Conclusion.** This new formula is the first quantitative approach for correcting hypervolaemic hypernatremia by achieving negative Na\(^+\) and K\(^+\) balance in excess of negative H\(_2\)O balance.

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Introduction

Hypernatremia is a common electrolyte disorder in hospitalized patients [1]. It is a disorder characterized by either an absolute or relative free water deficit. In hypovolaemic or euvolemic hypernatremia, there is an absolute free water deficit characterized by the negative mass balance of H\(_2\)O (\(V_{\text{MB}}\)) (Table 1) [2]. Therefore, treatment of these clinical disorders is targeted at replacement of the free water deficit with hypotonic intravenous fluids. In contrast, hypervolaemic hypernatremia is caused by an increase in total exchangeable Na\(^+\) and K\(^+\) in excess of the increment in total body water (TBW), resulting in a relative free water deficit [2]. Although these patients are hypervolaemic, they have a relative free water deficit because they develop a positive mass balance of Na\(^+\) and K\(^+\) (\(E_{\text{MB}}\)) in excess of the positive mass balance of H\(_2\)O (\(V_{\text{MB}}\)). Since these patients are hypervolaemic and hypernatremic, treatment of these patients should be targeted at both the correction of the hypernatremia and the attainment of a negative H\(_2\)O balance. Toward this goal, intravenous 5% dextrose (IV D5W) and furosemide can be utilized to correct the hypernatremia as well as to achieve negative H\(_2\)O balance. In this article, we derived a new equation to help guide the correction of hypervolaemic hypernatremia by inducing negative Na\(^+\) and K\(^+\) balance in excess of negative H\(_2\)O balance.

**Derivation of a new formula for correction of hypervolaemic hypernatremia by inducing negative Na\(^+\) and K\(^+\) balance in excess of negative water balance**

Based on the empirical relationship between the plasma water sodium concentration (\([\text{Na}\(^+\)]_{\text{pw}}\)) and the total exchangeable sodium (\(N_a\)), total exchangeable potassium (\(K_a\)) and total body H\(_2\)O (TBW) originally demonstrated by
Edelman et al. [3], we previously derived the Nguyen–Kurtz equation to predict the effect of simultaneous changes in the mass balance of Na\(^+\), K\(^+\) and H\(_2\)O and an increase in the plasma glucose concentration ([Na}\(^+\)]\(_p\)) in a given patient [4]:

\[
[\text{Na}\(^+\)]_{p2} = \frac{([\text{Na}\(^+\)]_{p1} + y_1)TBW_1 + 1.03 \times E_{MB}}{TBW_1 + V_{MB}} - y_2, 
\]

where

\[
y = 23.8 + (1.6/100)[(G) - 120] \\
[\text{Na}\(^+\)]_{p1} = \text{Initial plasma [Na}\(^+\)] \\
[\text{Na}\(^+\)]_{p2} = \text{Targeted plasma [Na}\(^+\)] \\
TBW_1 = \text{Initial total body water} \\
[E] = [\text{Na}\(^+\) + K\(^+\)] \\
\text{Input} = \text{non-infusate input} \\
\text{Output} = \text{non-renal output} \\
E_{MB} = \text{mass balance of Na}\(^+\) + K\(^+\) in a chosen duration of time \\
= [E]_{IVF} \times V_{IVF} + [E]_{input} \times V_{input} \\
- [E]_{output} \times V_{output} - [E]_{urine} \times V_{urine}
\]

\[
V_{MB} = \text{mass balance of H}_2\text{O in a chosen duration of time} \\
= V_{IVF} + V_{input} - V_{output} - V_{urine} \\
[G] = \text{plasma glucose concentration}
\]

Rearranging Equation 1,

\[
[\text{Na}\(^+\)]_{p2} + y_2 = \frac{([\text{Na}\(^+\)]_{p1} + y_1)TBW_1 + 1.03 \times ([E]_{IVF} \times V_{IVF} + [E]_{input} \times V_{input} - [E]_{output} \times V_{output} - [E]_{urine} \times V_{urine})}{TBW_1 + V_{MB}}
\]

Since IV D5W is the infusate used to correct hypervolaemic hypernatraemia, [E]_{IVF} = 0 and V_{urine} = V_{IVF} + V_{input} - V_{output} - V_{MB}, rearranging Equation 2,

\[
[\text{Na}\(^+\)]_{p2} + y_2 = \frac{([\text{Na}\(^+\)]_{p1} + y_1)TBW_1 + 1.03 \times ([E]_{input} \times V_{input} - [E]_{output} \times V_{output} - [E]_{urine} \times (V_{IVF} + V_{input} - V_{output} - V_{MB}))}{TBW_1 + V_{MB}}
\]

Rearranging Equation 3,

\[
([\text{Na}\(^+\)]_{p2} + y_2) \times (TBW_1 + V_{MB}) - ([\text{Na}\(^+\)]_{p1} + y_1) \\
\times TBW_1 - 1.03 \times ([E]_{input} \times V_{input} - [E]_{output} \times V_{output} \\
- [E]_{urine} \times (V_{input} - V_{output} - V_{MB})) = -1.03([E]_{urine} \times V_{IVF}) 
\]

Rearranging Equation 4,

\[
V_{IVF} = \frac{([\text{Na}\(^+\)]_{p1} + y_1) \times TBW_1 - ([\text{Na}\(^+\)]_{p2} + y_2)(TBW_1 + V_{MB}) + 1.03([E]_{input} \times V_{input} - [E]_{output} \times V_{output} \\
- [E]_{urine}(V_{input} - V_{output} - V_{MB}))/1.03 \times [E]_{urine}}{1.03 \times [E]_{urine}} 
\]

In patients with euglycaemia, Equation 5 can be simplified as follows:

\[
V_{IVF} = \frac{([\text{Na}\(^+\)]_{p1} + 23.8) \times TBW_1 - ([\text{Na}\(^+\)]_{p2} + 23.8)(TBW_1 + V_{MB}) + 1.03([E]_{input} \times V_{input} \\
- [E]_{output} \times V_{output} - [E]_{urine}(V_{input} - V_{output} \\
- V_{MB}))/1.03 \times [E]_{urine}}{1.03 \times [E]_{urine}} 
\]

**Discussion**

The mechanisms underlying the generation of hypernatraemia can be characterized according to the mass balance of Na\(^+\) and K\(^+\) (E_{MB}) in relation to the mass balance of H\(_2\)O (V_{MB}) (Table 1) [2]. In hypovolaemic hypernatraemia, the negative V_{MB} is the cause of the hypernatraemia, 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}. In these patients, a defect in the thirst mechanism or inadequate access to H\(_2\)O contributes to the negative V_{MB}. In euvolemic hypernatraemia, the negative V_{MB} is also the cause of the hypernatraemia, and E_{MB} is negligible in these patients. Although these patients actually have a negative V_{MB}, they appear clinically euvolaemic because only a small fraction of the total water loss originates from the intravascular space due to the negligible E_{MB}. In contrast, in hypervolaemic hypernatraemia, it is the positive E_{MB} that is the cause of the hypernatraemia (rather than negative V_{MB}); the positive V_{MB} in these patients would tend to lower the [Na]\(^+\)]_{p} but is not of sufficient magnitude to prevent the [Na]\(^+\)]_{p} from increasing. In this setting, the compensatory V_{MB} is inadequate due to a defect in the thirst mechanism or inadequate access to H\(_2\)O.

Hypervolaemic hypernatraemia is therefore caused by an increase in total exchangeable Na\(^+\) and K\(^+\) in excess of the increment in TBW, resulting in a relative free water deficit [2]. Treatment of hypervolaemic hypernatraemia can be therapeutically challenging since the infusion of IV D5W alone will correct the hypernatraemia at the expense of worsening volume overload, whereas the administration of furosemide alone will treat the hypervolaemia at the
The patient was aggressively diuresed with intravenous furosemide. On Day 4 of her admission, she was noted to have a sodium of 150 mmol/L, but also, there is an additional requirement to achieve a negative water balance to correct the increment in TBW. These seemingly conflicting therapeutic goals are typically approached by administering intravenous D5W (IV D5W) and furosemide to correct the hypernatraemia as well as to achieve negative water balance. Currently, there is no quantitative approach to predicting the volume of IV D5W (IVF) that needs to be administered that satisfies these requirements. Therefore, based on the principle of mass balance and the empirical relationship between exchangeable sodium, potassium, TBW and the plasma sodium concentration [3,4], we derived Equation 5 to help guide the correction of hypervolaemic hypernatraemia by inducing negative sodium and potassium balance in excess of negative water balance. Equation 5 calculates the volume of IV D5W (IVF) needed to lower the plasma sodium concentration ([Na\(^+\)]\(p\)) to a targeted level ([Na\(^+\)]\(p\)) by achieving the desired amount of negative water balance (V\(MB\)). Since Equation 5 determines the volume of IV D5W required to lower the [Na\(^+\)]\(p\) as well as to attain the desired negative V\(MB\), it is implicit in the derivation of this equation that the negative mass balance of sodium and potassium (E\(MB\)) must be in excess of the negative mass balance of water (V\(MB\)). In other words, the negative E\(MB\) must be greater than the negative V\(MB\) in order for the [Na\(^+\)]\(p\) to be lowered in the setting of the negative V\(MB\) (Figure 1).

Clinical utility of Equation 5

The utility of Equation 5 can be demonstrated in the following clinical case example: a 92-year-old Caucasian female with a history of congestive heart failure (CHF) secondary to diastolic dysfunction (ejection fraction 65%), hypertension and paroxysmal atrial fibrillation was admitted with recurrent symptoms of CHF. The patient reported four days of shortness of breath, orthopnea, paroxysmal nocturnal dyspnea and increasing lower extremity edema. Physical examination is significant for jugular venous pressure ~12 cm, bibasilar crackles and 2+ peripheral edema. The patient was aggressively diuresed with intravenous furosemide. On Day 4 of her admission, she was noted to have a [Na\(^+\)]\(p\) = 150 mmol/L, however, she remained symptomatic with her CHF, and chest X-ray revealed cardiomegaly and persistent pulmonary oedema and interstitial hydrostatic pulmonary oedema with small bilateral pleural effusions.

The renal service was consulted to help guide the management of the hypernatraemia in the setting of persistent pulmonary oedema. The patient's hypernatraemia was thought to be secondary to inadequate free H\(_2\)O replacement in the setting of hypotonic urinary losses resulting from the aggressive diuresis. Since the patient was both hypernatraemic and hypervolaemic, intravenous D5W (IV D5W) was administered to correct the hypernatraemia and furosemide was continued to achieve the negative water balance. Importantly, the goal of therapy was to administer the required volume of IV D5W (IVF) needed to lower the [Na\(^+\)]\(p\) from 150 mmol/L to 140 mmol/L while achieving the targeted 2 L of negative H\(_2\)O balance.

Parameters entered into Equation 5:

\[
\begin{align*}
\text{[Na}^+\text{]}_{p1} &= 150 \text{ mmol/L} \\
\text{[Na}^+\text{]}_{p2} &= 140 \text{ mmol/L} \\
\text{TBW}_1 &= 30 \text{ L} \\
V_{MB} &= -2 \text{ L} \\
\text{[Na}^+\text{ + K}^+]_{\text{urine}} &= 80 \text{ mmol/L}
\end{align*}
\]
According to Equation 5A, 5.6 L of IV D5W would be required to lower the $[\text{Na}^+]_p$ from 150 mmol/L to 140 mmol/L while achieving the desired 2 L of negative H$_2$O balance. Therefore, furosemide drip was titrated to attain a total urinary output of $\sim$7.6 L ($V_{\text{MB}} = 5.6\text{ L} - 7.6\text{ L} = -2\text{ L}$). Since the $[\text{Na}^+]_p$, decreased from 150 mmol/L to 140 mmol/L despite being in negative H$_2$O balance, the negative mass balance of Na$^+$ and K$^+$ ($E_{\text{MB}}$) must be in excess of the negative mass balance of H$_2$O ($V_{\text{MB}}$). The $E_{\text{MB}}$ in this case was $-608\text{ mmol}$ ($E_{\text{MB}} = [E]_{\text{IVF}} \times V_{\text{IVF}} - [E]_{\text{urine}} = 0 - 80 \times 7.6 = -608\text{ mmol}$). Consequently, the net fluid loss resulting from the negative mass balance of Na$^+$, K$^+$ and H$_2$O was hypertonic ($E_{\text{MB}}/V_{\text{MB}} = -608\text{ mmol}/-2\text{ L} = 304\text{ mmol/L}$) to the patient’s $[\text{Na}^+]_p$, thereby resulting in a decrement in the $[\text{Na}^+]_p$. This can also be verified by the known empirical relationship between the $[\text{Na}^+]_p$ and the exchangeable Na$^+$ ($Na_e$), exchangeable K$^+$ ($K_e$) and TBW [3,5]:

$$[\text{Na}^+]_p = \frac{1.03(Na_e + K_e)}{TBW} - 23.8. \quad (6)$$

Therefore:

$$Na_e + K_e = \frac{([\text{Na}^+]_p + 23.8) \times TBW}{1.03}. \quad (7)$$

$$Nae_1 + Ke_1 = (150 + 23.8) \times 30/1.03 = 5062\text{ mmol}$$
$$Nae_2 + Ke_2 = Nae_1 + Ke_1 + E_{\text{MB}} = 5062 - 608 = 4454\text{ mmol}$$
$$TBW_2 = TBW_1 + V_{\text{MB}} = 30 - 2 = 28\text{ L}.$$

Therefore,

$$[\text{Na}^+]_{p_2} = \frac{1.03(Na_{e_2} + K_{e_2})}{TBW_2} - 23.8$$
$$[\text{Na}^+]_{p_2} = \frac{1.03(4454)}{28} - 23.8 = 140\text{ mmol/L}$$

Therefore, Equation 5A accurately determines the volume of IV D5W ($V_{\text{IVF}}$) needed to lower the $[\text{Na}^+]_p$ from 150 mmol/L to 140 mmol/L while achieving the desired 2 L of negative H$_2$O balance.

**Etiologies of hypervolaemic hypernatraemia**

Hypervolaemic hypernatraemia is typically iatrogenic in etiology. Hypervolaemic hypernatraemia is often induced by the administration of hypertonic sodium-containing solutions. Examples include massive ingestion of a highly concentrated saline emetic or gargle, accidental or non-accidental salt poisoning in infants and young children and the infusion of hypertonic sodium bicarbonate to treat metabolic acidosis [6–8]. More commonly, hypervolaemic hypernatraemia is induced by the inappropriate replacement of hyponatric fluid losses with an infusate containing a higher sodium concentration [9]. Indeed, Kahn reported that hypervolaemic hypernatraemia often results from the replacement of hyponatric fluid losses (hyponatric fluid losses via sweat, gastric aspiration, diarrhea and diuretics) with isotonic saline in subjects with salt-retaining states [9]. In all these clinical scenarios, treatment of the hypervolaemic hypernatraemia necessitates the induction of a negative Na$^+$ and K$^+$ balance in excess of the negative H$_2$O balance in order to ameliorate both the hypernatraemia and the hypervolaemic state.

**Hyperglycaemic states**

In the setting of hyperglycaemia, Equation 5 must be utilized instead of Equation 5A to guide the treatment of hypervolaemic hypernatraemia. It is well known that there is an expected decrease of 1.6 mmol/L in the plasma $[\text{Na}^+]$ for each 100 mg/dL increment in the plasma glucose concentration resulting from the dilutional effect of hyperglycaemia induced by the translocation of water [10]. Therefore, in hyperglycaemic states, the severity of the hypernatraemia is often unrecognized due to the dilutional effect of hyperglycaemia on the plasma $[\text{Na}^+]$. In this setting, the severity of the hypernatraemia is often unmasked with correction of the hyperglycaemia.

Importantly, we have previously demonstrated that the $y$-intercept in Equation 6 is not constant and will vary predictably with the plasma glucose concentration [2,4,5]. Moreover, we have previously shown [2,4,5] that the plasma $[\text{Na}^+]$ varies with the plasma glucose concentration according to Equation 8:

$$[\text{Na}^+]_p = 1.03(Na_{e} + K_{e})/TBW$$
$$- 23.8 - (1.6/100)([G] - 120). \quad (8)$$

Equation 5, therefore takes into consideration the dilutional effect of hyperglycaemia on the plasma $[\text{Na}^+]$ by accounting for the fact that the $y$-intercept, $y = 23.8 + (1.6/100)([G] - 120)$, is not constant and will vary predictably with the plasma glucose concentration [2,4,5].

In hyperglycaemia, the glucosuria-induced osmotic diuresis will also lead to the urinary excretion of H$_2$O in excess of Na$^+$ + K$^+$, resulting in increased urinary electrolyte-free water excretion [11]. The increased urinary electrolyte-free water excretion induced by glucosuria will in turn lead to exacerbation of the underlying hypernatraemia. In diabetic patients, oral water replacement may therefore be preferable to IV D5W to avoid hyperglycaemia. However, in patients who are on bowel rest (NPO), IV D5W can be used with close monitoring of the plasma glucose concentration and tight control of the diabetes.

**Limitations of Equation 5**

There are limitations that one has to take into account when using Equation 5. First, one must take into consideration the fact that there may be dynamic changes in the mass balance of Na$^+$, K$^+$ and H$_2$O during treatment. Therefore, the patient’s input and output of Na$^+$, K$^+$, H$_2$O and the plasma $[\text{Na}^+]$ must be monitored frequently to guide further adjustments in the fluid prescription. The frequency with which this needs to be done will be determined by the clinical course and constancy of input and output sources in a given patient. Finally, the accuracy of Equation 5 is dependent on an accurate estimate of the
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In this regard, the regression equations reported by Watson \textit{et al.} can be used to provide an accurate estimate of TBW [12].

**Conclusion**

In summary, hypervolaemic hypernatraemia is caused by an increase in total exchangeable Na\(^+\) and K\(^+\) in excess of the increment in TBW, resulting in a relative free water deficit. Since these patients are hypernatraemic and hypervolaemic, treatment needs to be targeted at correcting not only the hypernatraemia but also to achieve a negative H\(_2\)O balance to correct the increment in TBW. In this setting, both intravenous D5W (IV D5W) and furosemide are administered to correct the hypernatraemia and to achieve a negative H\(_2\)O balance. Therefore, correction of hypervolaemic hypernatraemia can be attained by ensuring that the negative Na\(^+\) and K\(^+\) balance exceeds the negative H\(_2\)O balance. In this article, we derived a new equation to predict the volume of IV D5W \((V_{IVF})\) that needs to be administered that satisfies these requirements. This new equation is the first quantitative approach for correcting hypervolaemic hypernatraemia by achieving negative Na\(^+\) and K\(^+\) balance in excess of negative H\(_2\)O balance. This new equation should be especially helpful in providing the clinician with a quantitative approach to the correction of this common disorder.

Conflict of interest statement. None declared.

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