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A New Quantitative Approach for Correcting Cirrhosis-Associated Hyponatremia by Inducing Negative Water Balance in Excess of Negative Sodium and Potassium Balance

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Abstract

Introduction: Hypervolemic hyponatremia due to cirrhosis is caused by an increment in total body water (TBW) in excess of an increase in total exchangeable sodium (Na^+) and potassium (K^+). Therefore, therapy is aimed at treating not only the hyponatremia but there is an additional requirement to treat the volume overload.

Methods: Correction of cirrhosis-associated hyponatremia can be achieved by ensuring that the negative water (H_2O) balance is in excess of the negative Na^+ and K^+ balance. This therapeutic approach can be attained by administering intravenous 3% sodium chloride (NaCl) and furosemide.

Results: Presently, there is no quantitative method for predicting the volume of IV 3% NaCl required to be infused in conjunction with furosemide that satisfies this therapeutic goal. Therefore, based on the empirical relationship between the plasma Na^+ concentration and exchangeable Na^+, K^+, and TBW, a new formula is derived to calculate the volume of IV 3% NaCl required to raise the plasma Na^+ concentration ($[Na^+]_{p1}$) to a targeted level ($[Na^+]_{p2}$) by attaining the desired amount of negative Na^+, K^+, and H_2O balance.

Conclusion: This new equation is the first quantitative approach for treating hypervolemic hyponatremia by attaining a negative H_2O balance in excess of negative Na^+ and K^+ balance. This formula is particularly useful in the treatment of cirrhosis-associated hyponatremia where there are limited therapeutic options.

Categories: Internal Medicine, Nephrology
Keywords: cirrhosis, dysnatremia, hypervolemia, hyponatremia, sodium

Introduction

Hyponatremia is a common electrolyte disorder in hospitalized patients [1]. Hypovolemic hyponatremia is a disorder of negative Na^+ and K^+ balance in excess of negative H_2O balance [2]. Therefore, correction of hypovolemic hyponatremia is aimed at repletion of the negative Na^+, K^+, and H_2O balance with isotonic saline. In contrast, euvolemic hyponatremia is a disorder characterized by excess total body water (TBW) and relatively neutral Na^+ and K^+ balance, whereas hypervolemic hyponatremia is caused by an increment in TBW in excess of an increase in total exchangeable Na^+ and K^+ [2]. Hence, treatment of euvolemic hyponatremia is targeted at achieving negative H_2O balance while maintaining neutral Na^+ and K^+ balance, whereas hypervolemic hyponatremia is treated by inducing negative mass balance of H_2O (V_{MB}) in excess of negative mass balance of Na^+ and K^+ (E_{MB}). Toward this goal, intravenous 3% NaCl and furosemide can be utilized to correct hypervolemic hyponatremia. In this article, a new formula is derived to guide the treatment of hypervolemic hyponatremia by targeting negative H_2O balance in excess of negative Na^+ and K^+ balance. This new formula provides the clinician with a quantitative approach to the treatment of cirrhosis-associated hyponatremia where there are limited therapeutic options.

Materials And Methods

Correction of cirrhosis-associated hyponatremia can be attained by ensuring that the negative H_2O balance is in excess of the negative Na^+ and K^+ balance. Based on the study by Edelman et al., the plasma water sodium concentration ($[Na^+]_{pw}$) is defined by the ratio of the total exchangeable sodium (Na_e), total

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exchangeable potassium (K_e), and TBW by the following equation: $[Na^+]_{pw}$ = 1.11 (Na_e + K_e) / TBW − 25.6 [3]. Importantly, the Edelman equation is a linear regression equation that is derived based on experimental data involving 98 patients [3]. Therefore, alterations in the mass balance of Na^+ and K^+ (E_{MB}) in relation to changes in the mass balance of H_2O (V_{MB}) will result in a change in the ratio (Na_e + K_e) / TBW, thereby altering the plasma water sodium concentration ($[Na^+]_{pw}$). In this article, a new formula is derived to guide the treatment of hypervolemic hyponatremia by targeting negative H_2O balance in excess of negative Na^+ and K^+ balance by administering intravenous hypertonic sodium chloride (3% NaCl) and furosemide. This new formula calculates the volume of 3% NaCl infused with furosemide required to raise the plasma sodium concentration ($[Na^+]_{p1}$) to a targeted level ($[Na^+]_{p2}$) by attaining negative H_2O balance in excess of negative Na^+ and K^+ balance.

Results

Derivation of a new equation for the treatment of hypervolemic hyponatremia by targeting negative H_2O balance in excess of negative Na^+ and K^+ balance

In 1958, Edelman et al. defined the empirical relationship between the plasma water sodium concentration ($[Na^+]_{pw}$) and the total exchangeable sodium (Na_e), total exchangeable potassium (K_e), and TBW [3]. Based on the Edelman equation, Nguyen previously derived a formula for predicting changes in the plasma sodium concentration ($[Na^+]_p$) resulting from simultaneous alterations in the mass balance of Na^+, K^+, and H_2O [4]:

$$[\mathrm{Na}^+]_{p2} = \frac{\left([\mathrm{Na}^+]_{p1} + 23.8\right)\mathrm{TBW}_1 + 1.03 \times E_{\mathrm{MB}}}{\mathrm{TBW}_1 + V_{\mathrm{MB}}} - 23.8 \quad \text{(Eq. 1)}$$

where $[Na^+]_{p1}$ indicates initial plasma $[Na^+]$; $[Na^+]_{p2}$ indicates targeted plasma [Na+]; TBW_1 indicates initial total body water; E_{MB} indicates mass balance of $Na^+ + K^+$ in a chosen duration of time.

$E_{MB} = [E]_{IVF} \times V_{IVF} + [E]_{input} \times V_{input} - [E]_{output} \times V_{output} - E]_{urine} \times V_{urine}$

V_{MB} indicates the mass balance of H_2O in a chosen duration of time

$V_{MB} = V_{IVF} + V_{input} - V_{output} - V_{urine}$

On rearranging Eq. 1,

$$[\mathrm{Na}^+]_{p2} + 23.8 = \frac{\left([\mathrm{Na}^+]_{p1} + 23.8\right)\mathrm{TBW}_1 + 1.03 \times E_{\mathrm{MB}}}{\mathrm{TBW}_1 + V_{\mathrm{IVF}} + V_{\mathrm{input}} - V_{\mathrm{output}} - V_{\mathrm{urine}}} \quad \text{(Eq. 2)}$$

where V represents the volume of a given fluid in a chosen duration of time; IVF represents intravenous fluid (infusate, i.e., 3% NaCl); input represents non-infusate input (other sources of input besides 3% NaCl); output represents non-renal output (other sources of output besides urine).

Previously, Nguyen derived an equation for the correction of hypervolemic hypernatremia by inducing negative Na^+ and K^+ balance in excess of negative H_2O balance [5]. In contrast, treatment of hypervolemic hyponatremia can be achieved by inducing a negative H_2O balance in excess of negative Na^+ and K^+ balance. This therapeutic approach can be attained by administering intravenous 3% NaCl and furosemide. Since IV 3% NaCl is the infusate needed to treat hypervolemic hyponatremia, $[E]_{IVF}$ = 513 mmol/L and

$V_{urine} = ([E]_{IVF} \times V_{IVF} + [E]_{input} \times V_{input} - [E]_{output} \times V_{output} - E_{MB}) / [E]_{urine}$, rearranging Eq. 2:

$$[\mathrm{Na}^+]_{p2} + 23.8 = \frac{\left([\mathrm{Na}^+]_{p1} + 23.8\right)\mathrm{TBW}_1 + 1.03 \times E_{\mathrm{MB}}}{\mathrm{TBW}_1 + V_{\mathrm{IVF}} + V_{\mathrm{input}} - V_{\mathrm{output}} - \frac{\left([E]_{\mathrm{IVF}} \times V_{\mathrm{IVF}} + [E]_{\mathrm{input}} \times V_{\mathrm{input}} - [E]_{\mathrm{output}} \times V_{\mathrm{output}} - E_{\mathrm{MB}}\right)}{[E]_{\mathrm{urine}}}}$$

(Eq. 3)

where $[E] = [Na^+ + K^+]$ = sodium and potassium concentration

On rearranging Eq. 3,

$$\mathrm{TBW}_1+V_{\mathrm{IVF}}+V_{\mathrm{input}}-V_{\mathrm{output}}-\frac{([E]_{\mathrm{IVF}}\times V_{\mathrm{IVF}}+[E]_{\mathrm{input}}\times V_{\mathrm{input}}-[E]_{\mathrm{output}}\times V_{\mathrm{output}}-E_{\mathrm{MB}})}{[E]_{\mathrm{urine}}}=\frac{\left(\left([\mathrm{Na}^+]_{p1}+23.8\right)\mathrm{TBW}_1+1.03\times E_{\mathrm{MB}}\right)}{[\mathrm{Na}^+]_{p2}+23.8}$$

(Eq. 4)

On rearranging Eq. 4,

$$V_{\mathrm{IVF}}-\left([E]_{\mathrm{IVF}}\times\frac{V_{\mathrm{IVF}}}{[E]_{\mathrm{urine}}}\right)=\frac{([Na^+]_{p1}+23.8)\,\mathrm{TBW}_1+1.03\times E_{\mathrm{MB}}}{([Na^+]_{p2}+23.8)}-\mathrm{TBW}_1-V_{\mathrm{input}}+V_{\mathrm{output}}+\frac{([E]_{\mathrm{input}}\times V_{\mathrm{input}}-[E]_{\mathrm{output}}\times V_{\mathrm{output}}-E_{\mathrm{MB}})}{[E]_{\mathrm{urine}}}$$

(Eq. 4A)

On rearranging Eq. 4A,

$$V_{\mathrm{IVF}}\left(1-\frac{[E]_{\mathrm{IVF}}}{[E]_{\mathrm{urine}}}\right)=\frac{([Na^+]_{p1}+23.8)\,\mathrm{TBW}_1+1.03\times E_{\mathrm{MB}}}{([Na^+]_{p2}+23.8)}-\mathrm{TBW}_1-V_{\mathrm{input}}+V_{\mathrm{output}}+\frac{([E]_{\mathrm{input}}\times V_{\mathrm{input}}-[E]_{\mathrm{output}}\times V_{\mathrm{output}}-E_{\mathrm{MB}})}{[E]_{\mathrm{urine}}}$$

(Eq. 4B)

On rearranging Eq. 4B,

$$V_{\mathrm{IVF}}=\frac{\frac{\left([Na^+]_{p1}+23.8\right)\mathrm{TBW}_1+1.03\times E_{\mathrm{MB}}}{([Na^+]_{p2}+23.8)}-\mathrm{TBW}_1-V_{\mathrm{input}}+V_{\mathrm{output}}+\frac{\left([E]_{\mathrm{input}}\times V_{\mathrm{input}}-[E]_{\mathrm{output}}\times V_{\mathrm{output}}-E_{\mathrm{MB}}\right)}{[E]_{\mathrm{urine}}}}{1-\frac{[E]_{\mathrm{IVF}}}{[E]_{\mathrm{urine}}}}$$

(Eq. 5)

Discussion

Hyponatremia is a common electrolyte disorder in hospitalized patients [1]. The mechanisms underlying the generation of hyponatremia are defined by alterations in the mass balance of Na^+ and K^+ (E_{MB}) in relation to changes in the mass balance of H_2O (V_{MB}) [2]. Hypervolemic hyponatremia is caused by an increment in TBW in excess of the increase in total exchangeable Na^+ and K^+, resulting in a relative free water excess [2]. Hypervolemic hyponatremia is commonly caused by congestive heart failure and cirrhosis. Given that hyponatremia due to congestive heart failure and cirrhosis is due to a relative free water excess, vasopressin 2-receptor antagonists, tolvaptan and conivaptan, respectively, can be used to treat hyponatremia in these clinical settings by inducing negative H_2O balance [6,7]. However, tolvaptan, a selective vasopressin 2-receptor antagonist, is contraindicated in cirrhosis-associated hyponatremia due to the potential risk of hepatotoxicity [8]. Moreover, conivaptan, a non-selective V1a and V2 receptor antagonist is typically avoided in cirrhotic patients since it can cause hypotension in these patients with baseline low blood pressure, and it may increase the risk of variceal bleeding and worsen underlying hepatorenal syndrome [6].

Treatment of hypervolemic hyponatremia can be therapeutically challenging in cirrhotic patients who are refractory to free water restriction and diuretic therapy and who are not candidates for vasopressin 2-receptor antagonists. In these patients with cirrhosis-associated hyponatremia, treatment of hypervolemic hyponatremia is aimed at correcting the hyponatremia as well as inducing negative Na^+, K^+, and H_2O balance to treat the volume overload. Toward this goal, the infusion of 3% NaCl with intravenous furosemide can be effective in treating both hyponatremia and volume overload by inducing negative H_2O balance in excess of negative Na^+ and K^+ balance.

Presently, there is no quantitative method for predicting the volume of IV 3% NaCl (V_{IVF}) required to be infused with furosemide that meets this goal. Based on the empirical interrelationship between the plasma water $[Na^+]$ and exchangeable sodium (Na_e), exchangeable potassium (K_e), and TBW as defined by the Edelman equation: $[Na^+]_{pw} = 1.11 (Na_e + K_e) / TBW - 25.6$ [3], alterations in the mass balance of Na^+ and K^+ (E_{MB}) in relation to changes in the mass balance of H_2O (V_{MB}) will result in a change in the ratio $(Na_e + K_e)$ / TBW, thereby altering the plasma water sodium concentration ($[Na^+]_{pw}$). Therefore, equation 5 is derived to guide the treatment of hypervolemic hyponatremia by targeting negative H_2O balance in excess of negative Na^+ and K^+ balance. Equation 5 determines the volume of IV 3% NaCl (V_{IVF}) required to raise the initial plasma Na^+ concentration ($[Na^+]_{p1}$) to the desired level ($[Na^+]_{p2}$) by inducing the targeted amount of negative Na^+ and K^+ balance (E_{MB}). Since equation 5 calculates the volume of IV 3% NaCl needed to raise the $[Na^+]_p$ as well as to achieve the targeted negative E_{MB}, the derivation of this equation accounts for the fact that the negative mass balance of H_2O (V_{MB}) must be in excess of the negative mass balance of Na^+ and

K^+ (E_{MB}). Simply put, in order for the $[Na^+]_p$ to be increased in the setting of negative E_{MB}, the negative V_{MB} must be greater than the negative E_{MB}.

Clinical utility of equation 5

To illustrate the clinical utility of equation 5, let's calculate the volume of IV 3% NaCl required to increase the $[Na^+]_p$ from 124 mmol/L to 130 mmol/L while attaining a targeted negative E_{MB} of -100 mmoles with furosemide in a 72 kg male with hypervolemic hyponatremia due to cirrhosis.

Parameters entered into equation 5 are: $[Na^+]_{p1}$ of 124 mmol/L; $[Na^+]_{p2}$ of 130 mmol/L; TBW_1 of 43.2 liters; E_{MB} of -100 mmoles; $[Na^+ + K^+]_{urine}$ = 80 mmol/L.

According to equation 5, 0.204 liters of IV 3% NaCl would be needed to raise the $[Na^+]_p$ from 124 mmol/L to 130 mmol/L while attaining the desired negative E_{MB} of -100 mmoles. Hence, furosemide drip was titrated to induce a total urinary output of ~2.56 liters (V_{urine} = ($[E]_{IVF}$ x V_{IVF} + $[E]_{input}$ x V_{input} - $[E]_{output}$ x V_{output} - E_{MB}) / $[E]_{urine}$ = 2.56 L). Given that the $[Na^+]_p$ increased from 124 mmol/L to 130 mmol/L in the setting of negative $Na^+ + K^+$ balance, the negative mass balance of H_2O (V_{MB}) must exceed the negative mass balance of Na^+ and K^+ (E_{MB}). The E_{MB} in this case was -100 mmol (E_{MB} = $[E]_{IVF}$ x V_{IVF} - $[E]_{urine}$ x V_{urine} = 513 x 0.204 - 80 x 2.56 = -100 mmol), and the V_{MB} was -2.36 L (V_{MB} = V_{IVF} - V_{urine} = 0.204 - 2.56 = -2.36 L). As a result, the net fluid loss resulting from the negative mass balance of Na^+, K^+, and H_2O was hypotonic (E_{MB} / V_{MB} = -100 mmol / -2.36 L= 42 mmol/L) to the patient's $[Na^+]_p$, thereby resulting in an increase in the $[Na^+]_p$. This can be verified by the empirical interrelationship between the $[Na^+]_p$ and the exchangeable Na^+ (Na_e), exchangeable K^+ (K_e), and TBW [9]:

$$[\mathrm{Na}^+]_p = \frac{1.03(\mathrm{Na}_e + \mathrm{K}_e)}{\mathrm{TBW}} - 23.8 \quad \text{(Eq. 6)}$$

Therefore,

$$\mathrm{Na}_e + \mathrm{K}_e = \frac{\left([\mathrm{Na}^+]_p + 23.8\right) \times \mathrm{TBW}}{1.03} \quad \text{(Eq. 7)}$$

$Na_{e1} + K_{e1}$ = (124 + 23.8) x 43.2 / 1.03 = 6199 mmol

$Na_{e2} + K_{e2}$ = $Na_{e1} + K_{e1} + E_{MB}$ = 6199 - 100 = 6099 mmol

TBW_2 = TBW_1 + V_{MB} = 43.2 - 2.36 = 40.84 liters

Therefore,

$$[\mathrm{Na}^+]_{p2} = \frac{1.03(\mathrm{Na}_{e2} + \mathrm{K}_{e2})}{\mathrm{TBW}_2} - 23.8$$

$$[\mathrm{Na}^+]_{p2} = \frac{1.03 \times 6099}{40.84} - 23.8 = 130\,\mathrm{mmol/L}$$

Therefore, equation 5 accurately calculates the volume of IV 3% NaCl (V_{IVF}) required to raise the $[Na^+]_p$ from 124 mmol/L to 130 mmol/L in conjunction with IV furosemide in achieving negative H_2O balance in excess of negative $Na^+ + K^+$ balance.

Aquaresis versus natriuresis

It is well known that furosemide induces a natriuresis, whereas tolvaptan induces an aquaresis, which results in a greater degree of electrolyte-free water clearance. In cirrhotic patients with hypervolemic hyponatremia in whom tolvaptan is contraindicated, the utility of IV 3% NaCl in conjunction with IV furosemide is an alternative approach to increase net electrolyte-free water clearance. As the targeted negative E_{MB} approaches zero, the net electrolyte-free water clearance increases accordingly and simulates the effect of tolvaptan. Using the clinical example above, the net electrolyte-free water clearance can be calculated at various targeted E_{MB} by using the whole-body electrolyte-free water clearance (WB-EFWC) formula [10]:

$$\text{WB-EFWC} = V_{\text{MB}} - \frac{1.03\,E_{\text{MB}}}{[\text{Na}^+]_p + 23.8} \text{ (Eq. 8)}$$

where WB-EFWC indicates whole-body electrolyte-free water clearance; $[Na^+]_p$ indicates plasma Na^+ concentration; E_{MB} indicates mass balance of $Na^+ + K^+ = [E]_{input} \times V_{input} - [E]_{output} \times V_{output}$; V_{MB} indicates mass balance of $H_2O = V_{input} - V_{output}$; $[E] = [Na^+ + K^+] = Na^+$ and K^+ concentration; V indicates volume.

Rather than considering only the renal component of electrolyte-free water clearance, this formula calculates the whole-body electrolyte-free water clearance for a given mass balance of Na^+, K^+, and H_2O by taking into account all sources of input and output of Na^+, K^+, and H_2O [10].

As shown in Table *1*, as the negative E_{MB} decreases in value from -250 mmoles to 0 mmole, the WB-EFWC increases, resulting in a greater degree of aquaresis. When the targeted E_{MB} is zero, the aquaresis results in a more effective correction of the hyponatremia, requiring only a negative V_{MB} of -1.68 L to raise the $[Na^+]_p$ from 124 mmol/L to 130 mmol/L. On the other hand, as the negative E_{MB} increases in value from 0 mmole to -250 mmoles, the WB-EFWC decreases, resulting in a greater degree of natriuresis. When the targeted E_{MB} is -250 mmoles, the natriuresis results in less effective correction of the hyponatremia, requiring a negative V_{MB} of -3.36 L to raise the $[Na^+]_p$ from 124 mmol/L to 130 mmol/L. However, the greater natriuresis will result in greater volume losses, thereby leading to more effective treatment of the volume overload. Therefore, the desired aquaresis versus natriuresis can be targeted based on the severity of the hyponatremia and the degree of volume overload.

Initial $[Na^+]_p$ (mmol/L)	Targeted $[Na^+]_p$ (mmol/L)	Initial TBW (L)	$[Na^+ + K^+]_{IVF}$ (mmol/L)	$[Na^+ + K^+]_{urine}$ (mmol/L)	V_{IVF} (L)	V_{urine} (L)	V_{MB} (L)	E_{MB} (mmol)	WB-EFWC (L)
124	130	43.2	513	80	0.311	1.997	-1.685	0	-1.685
124	130	43.2	513	80	0.258	2.278	-2.020	-50	-1.672
124	130	43.2	513	80	0.204	2.559	-2.355	-100	-1.658
124	130	43.2	513	80	0.151	2.840	-2.690	-150	-1.645
124	130	43.2	513	80	0.097	3.122	-3.025	-200	-1.631
124	130	43.2	513	80	0.043	3.403	-3.360	-250	-1.617

TABLE 1: Aquaresis versus natriuresis

$[Na^+]_p$: plasma Na^+ concentration; TBW: total body water; $[Na^+ + K^+]_{IVF}$: infusate sodium and potassium concentration; $[Na^+ + K^+]_{urine}$: urinary sodium and potassium concentration; V_{IVF}: infusate volume; V_{urine}: urinary volume; V_{MB}: mass balance of H_2O; E_{MB}: mass balance of $Na^+ + K^+$; WB-EFWC: whole-body electrolyte-free water clearance

Limitations of equation 5

There are several limitations inherent in Eq. 5 that need to be considered in the treatment of patients with hypervolemic hyponatremia. First, given that there may be dynamic changes in the mass balance of Na^+, K^+, and H_2O during therapy, the patient's input and output of Na^+, K^+, and H_2O and the plasma $[Na^+]$ must be monitored closely to guide additional adjustments in the fluid prescription. The constancy of input and output sources in any given patient will determine the frequency with which this needs to be done. Last, since TBW is a variable in Eq. 5, the accuracy of Eq. 5 relies on an accurate estimate of TBW. In this context, the regression equations reported by Watson et al. can be used to obtain an accurate estimate of TBW [11].

Conclusions

In conclusion, hypervolemic hyponatremia due to cirrhosis is caused by an increment in TBW in excess of an increase in total exchangeable Na^+ and K^+, resulting in a relative free water excess. Since these patients are hypervolemic and hyponatremic, therapy is aimed at correcting not only the hyponatremia but also attaining negative Na^+, K^+, and H_2O balance. Therefore, correction of hypervolemic hyponatremia can be attained by administering intravenous 3% NaCl and furosemide to achieve a negative H_2O balance in excess of negative Na^+ and K^+ balance. In this article, a new formula is derived to determine the volume of IV 3% NaCl (V_{IVF}) that needs to be infused that fulfills these requirements. Importantly, this new equation is derived based on the Edelman equation, which is a linear regression equation that is determined based on experimental data involving 98 patients. This new formula is the first quantitative approach for treating hypervolemic hyponatremia by attaining a negative H_2O balance in excess of negative Na^+ and K^+ balance. This new formula will be particularly helpful in providing the clinician with a quantitative method for the correction of cirrhosis-associated hyponatremia where there are limited therapeutic options.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Minhtri K. Nguyen

Acquisition, analysis, or interpretation of data: Minhtri K. Nguyen, Minh-Kevin Nguyen, Dhiresh Bandaru

Drafting of the manuscript: Minhtri K. Nguyen, Minh-Kevin Nguyen, Dhiresh Bandaru

Critical review of the manuscript for important intellectual content: Minhtri K. Nguyen

Supervision: Minhtri K. Nguyen

Disclosures

Human subjects: All authors have confirmed that this study did not involve human participants or tissue. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Upadhyay A, Jaber BL, Madias NE: Incidence and prevalence of hyponatremia . Am J Med. 2006, 119:S30-5. 10.1016/j.amjmed.2006.05.005
2. Nguyen MK, Kurtz I: New insights into the pathophysiology of the dysnatremias: a quantitative analysis . Am J Physiol Renal Physiol. 2004, 287:F172-80. 10.1152/ajprenal.00106.2004
3. Edelman IS, Leibman J, O'Meara MP, Birkenfeld LW: Interrelations between serum sodium concentration, serum osmolarity and total exchangeable sodium, total exchangeable potassium and total body water. J Clin Invest. 1958, 37:1236-56. 10.1172/JCI103712
4. Kurtz I, Nguyen MK: A simple quantitative approach to analyzing the generation of the dysnatremias . Clin Exp Nephrol. 2003, 7:138-43. 10.1007/s10157-003-0234-2
5. Nguyen MK, Kurtz I: Correction of hypervolaemic hypernatraemia by inducing negative Na+ and K+ balance in excess of negative water balance: a new quantitative approach. Nephrol Dial Transplant. 2008, 23:2223-7. 10.1093/ndt/gfm932
6. Greenberg A, Verbalis JG: Vasopressin receptor antagonists. Kidney Int. 2006, 69:2124-30. 10.1038/sj.ki.5000432
7. Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH: Hyponatremia treatment guidelines 2007: expert panel recommendations. Am J Med. 2007, 120:S1-21. 10.1016/j.amjmed.2007.09.001
8. FDA Drug Safety Communication: FDA limits duration and usage of Samsca (tolvaptan) due to possible liver injury leading to organ transplant or death. (2013). https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-limits-duration-and-usage-sa....
9. Nguyen MK, Kurtz I: A new quantitative approach to the treatment of the dysnatremias . Clin Exp Nephrol. 2003, 7:125-37. 10.1007/s10157-003-0233-3
10. Nguyen MK, Kurtz I: Whole-body electrolyte-free water clearance: derivation and clinical utility in analyzing the pathogenesis of the dysnatremias. Clin Exp Nephrol. 2006, 10:19-24. 10.1007/s10157-005-0395-2
11. Watson PE, Watson ID, Batt RD: Total body water volumes for adult males and females estimated from simple anthropometric measurements. Am J Clin Nutr. 1980, 33:27-39. 10.1093/ajcn/33.1.27