

Hypothesis

Current prescriptions for the correction of hyponatraemia and hypernatraemia: are they too simple?

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Abstract

Hypo- and hypernatraemic (dysnatraemic) disorders are among the most common electrolyte disorders encountered by primary care providers and nephrologists. They represent a diagnostic and therapeutic challenge, and inappropriate management can result in serious sequelae. Several formulas addressing the fluid prescription for dysnatraemic patients have been introduced. Many authors stress the importance of considering output as well as input in formulating a treatment plan for the dysnatraemic patient. However, currently available formulas fail to account for ongoing renal and extrarenal fluid and electrolyte losses. We propose a novel, versatile formula based on established principles governing the distribution of Na⁺ in body fluids. The formula can be used in a simplified form for a quick but accurate estimate of the change in serum [Na⁺] for any infused fluid, while simultaneously accounting for renal losses. The formula can also be expanded to include more complex losses if desired. Importantly, it forces the caregiver to consider both output and input when formulating a prescription for the dysnatraemic patient.

Keywords: fluid prescription; formula; hypernatraemia; hyponatraemia

Introduction

Both hyponatraemia and hypernatraemia (dysnatraemias) are among the most common electrolyte disorders encountered by primary care providers and nephrologists in the inpatient and outpatient settings. Both disorders can cause significant morbidity and even mortality [1,2]. In addition to being diagnostic

dilemmas, they also represent a management challenge. Undercorrection, overcorrection or too rapid correction can result in significant neurological impairment and prolonged hospitalization [1–4]. For these reasons, many formulas addressing qualitative and quantitative fluid replacement strategies have emerged in an attempt to provide appropriate fluid management.

Three conventional formulas are currently used to estimate the Na⁺ and water deficits for hyponatraemic and hypernatraemic states, respectively [5–7]:

$$\text{Water deficit} = \text{TBW} [(\text{current serum } [\text{Na}^+] / 140) - 1] \quad (1)$$

$$\text{Water excess} = \text{TBW} - [\text{TBW} \times (\text{current serum } [\text{Na}^+] / 140)] \quad (2)$$

$$\text{Na}^+ \text{ deficit} = \text{TBW} (\text{desired serum } [\text{Na}^+] - \text{current serum } [\text{Na}^+]) \quad (3)$$

where TBW = total body water. These formulas provide an estimate of pre-existing water deficits or excesses, but do not specifically guide the physician regarding the composition or the infusion rate of a particular solution. For this reason, Adroge and Madias [8] introduced a formula derived from established principles governing the distribution of Na⁺ in body fluids. Unlike its predecessors, this formula allows one to calculate the impact of the intravenous infusion of 1 l of any solution on serum Na⁺ concentration in mEq/l:

$$\Delta \text{Serum } [\text{Na}^+] = ([\text{Na}^+]_{\text{inf}} - [\text{Na}^+]_{\text{s}}) / (\text{TBW} + 1) \quad (4)$$

where $\Delta \text{Serum } [\text{Na}^+]$ is the change in serum Na⁺ concentration, $[\text{Na}^+]_{\text{inf}}$ is the concentration of infusate Na⁺, and $[\text{Na}^+]_{\text{s}}$ is the current serum Na⁺ concentration.

Equation 4 clearly has many advantages. It is simple, easy to use, and requires little data. It is also a dynamic formula, which can be used repeatedly to reassess the patient as often as needed. Importantly,

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it is applicable to both hyponatraemic and hypernatraemic states. As this formula does not account for the cation contribution of K^+ in the infusate, however, it was recently revised:

$$\Delta\text{Serum } [Na^+] = ([Na^+ + K^+]_{\text{inf}} - [Na^+]_s) / (TBW + 1) \quad (5)$$

While clearly helpful, this formula is limited because the patient is approached as a closed system and it fails to account for concurrent water and electrolyte losses from the kidneys, gastrointestinal tract, skin and lungs. To paraphrase Albert Einstein, it is good to make things simple, but not too simple. The pitfalls of Equation 5 are illustrated in the following hypothetical case.

Case 1

A 68-year-old male weighing 73 kg was admitted to hospital with mesencephalic subarachnoid haemorrhage. Initially he did well, but on hospital day 5 was noted to be drowsy, difficult to wake and disoriented. On physical examination he appeared to be in mild distress. Vital statistics were: temperature 36.8°C; blood pressure (BP) 110/60 mmHg and heart rate (HR) 100 beats/min lying down, and BP 90/48 mmHg and HR 122 beats/min sitting; respiratory rate (RR) 18 breaths/min; and weight 70 kg. His physical examination was otherwise notable for dry mucous membranes, absent jugular venous distension and no peripheral oedema. Neurological examination revealed him to be remarkable for lethargy and drowsiness, but was otherwise non-focal. Review of fluid input and output records revealed a daily urine output of 3–4 l, with an overall negative balance of 3.5 l over 3 days. Prior to his decompensation the patient had been tolerating a low-fat diet with a daily allowance of 2 g Na, but for the past 3 days had not been eating; nor had he received i.v. fluids. A head computerized tomography scan showed no change from admission. Transcutaneous dopplers revealed mild cerebral vasospasm. Laboratory data and pertinent calculations are shown in Table 1.

The patient was hypovolaemic as evidenced by his orthostatic changes, physical examination, negative fluid balance and weight loss (3 kg). He presented with hypo-osmolar hyponatraemia with a high urinary Na^+ and osmolality. This clinical presentation is compatible with cerebral salt wasting syndrome [9]. Using Equation 5, the calculated change in serum $[Na^+]$ for every litre of normal saline supplemented with 40 mEq K^+ would be 1.8 mEq/l. The desired increase in serum $[Na^+]$ is 0.5 mEq/l/h or 12 mEq/day. The volume of fluid needed to achieve the desired increase in serum $[Na^+]$ at the appropriate rate of correction is therefore 6.6 l, given at a rate of 275 ml/h. The patient was given the prescribed fluids at the appropriate rate, but 24 h later he was noted to be more obtunded and his serum $[Na^+]$ had fallen to 113 mEq/l.

Table 1. Case laboratory data and calculations

	Case 1	Case 2
Serum		
$[Na^+]$ (mEq/l)	116	120
$[K^+]$ (mEq/l)	3.2	3.1
$[Cl^-]$ (mEq/l)	86	91
$[HCO_3^-]$ (mEq/l)	28	29
BUN (mg/dl)	23	17
Creatinine (mg/dl)	1.4	1.1
Osmolality (mmol/kg H_2O)	260	260
TBW (l)	42	42
V_i (l)	1	1
$[Na^+]_{\text{inf}}$ (mEq/l)	154	154
$[K^+]_{\text{inf}}$ (mEq/l)	40	80
V_u (l/day)	3.5	1
$[Na^+]_u$ (mEq/l)	234	17
$[K^+]_u$ (mEq/l)	60	12
U_{osm} (mmol/kg H_2O)	720	210
V_o (l/day)	N/A	3
$\Delta V = V_i - (V_u + V_o)$ (l/day)	-2.5	-3
$[Na^+]_o$ (mEq/l)	N/A	30
$[K^+]_o$ (mEq/l)	N/A	25
$\Delta\text{Serum } [Na^+]$ (mEq/l)		
Using Equation 5	1.8	2.65
Using Equation 8	-2.3	4.8
Using Equation 7	-13.7	4.8
Using Equation 9	N/A	10.25

V_i , volume of infusate; $[Na^+]_{\text{inf}}$, infusate Na^+ concentration; $[K^+]_{\text{inf}}$, infusate K^+ concentration; V_u , urine volume/day; $[Na^+]_u$, spot urine $[Na^+]$; $[K^+]_u$, spot urine $[K^+]$; U_{osm} , urine osmolality; V_o , extra-renal fluid losses; $[Na^+]_o$, extra-renal Na^+ output; $[K^+]_o$, extra-renal K^+ output.

Results

The use of Equation 5 for case 1 results in a significant overestimation of the rate of correction of serum $[Na^+]$ because it fails to account for ongoing urine electrolyte losses. We have therefore derived a formula that accounts for renal and extrarenal Na^+ and K^+ losses, using the mathematical model of Adroge and Madias [8]. In a steady state, provided there is no elevation in body temperature, the sum of internal water production through oxidation and the water contained in food equals the insensible water loss from skin and lungs as well as water loss from stools; therefore these inputs and outputs can be safely ignored [6,10]. Also, unless the patient is in a hot climate, is exercising vigorously or is febrile, fluid and electrolyte losses in sweat are minimal [10]. Similarly, gastrointestinal losses of water and Na^+ are also minimal provided the patient does not have vomiting, diarrhoea or ostomy output. Therefore, under most circumstances, only urinary Na^+ and K^+ excretion will have a significant impact on serum $[Na^+]$. For this reason, the proposed formula will address primarily urinary electrolyte losses, but it can be readily adjusted for extrarenal losses. Using the same mathematical model of Adroge and Madias, our formula is:

$$\Delta\text{Serum } [Na^+] = \{ (V_i)[Na^+]_{\text{inf}} - (V_u)[Na^+]_u - (\Delta V)[Na^+]_s \} / [TBW + (\Delta V)] \quad (6)$$

where V_i is the volume of infusate in litres, V_u is the urine output in litres, ΔV is $V_i - V_u$, $[\text{Na}^+]_{\text{inf}}$ is the Na^+ concentration in the infusate, $[\text{Na}^+]_u$ is the urinary Na^+ concentration, $[\text{Na}^+]_s$ is the current serum Na^+ concentration and TBW is the total body water. For details regarding the derivation of this and subsequent formulae, please refer to the Appendix.

To account for the contribution K^+ input or output, the formula becomes:

$$\Delta \text{Serum } [\text{Na}^+] = \{(V_i)[\text{Na}^+ + \text{K}^+]_{\text{inf}} - (V_u)[\text{Na}^+ + \text{K}^+]_u - (\Delta V)[\text{Na}^+]_s\} / [\text{TBW} + (\Delta V)] \quad (7)$$

It should be noted that in the absence of any output the formula reduces to Equation 5.

Although more detailed than Equation 5, when input equals output, Equation 7 simplifies to:

$$\Delta \text{Serum } [\text{Na}^+] = (V_i[\text{Na}^+ + \text{K}^+]_{\text{inf}} - V_u[\text{Na}^+ + \text{K}^+]_u) / \text{TBW} \quad (8)$$

Discussion

In such a simplified form, Equation 8 can be used to quickly estimate the change in $[\text{Na}^+]_s$ for a given volume of infusate, assuming an equal volume of urine output. This would be particularly helpful when one is trying to replace urine output millilitre for millilitre while trying to correct serum $[\text{Na}^+]$. Perhaps just as importantly, using either Equation 7 or 8 obliges one to consider the impact of urinary cation losses and thus optimize patient management. If we reconsider Case 1 and use Equation 8 during the patient's initial management, an entirely different fluid prescription is obtained. Since the patient's daily urine output is unknown at the outset, Equation 8 can be used initially to calculate the change in Na^+ based on 1 l of infusate and 1 l of urine output. Based on Equation 8, this patient's serum $[\text{Na}^+]$ would be predicted to decrease by 2.3 mEq/l with the infusion of 1 l of normal saline supplemented with 40 mEq of K^+ (unlike the increase of 1.8 mEq/l predicted using Equation 5). Once his daily urine output of 3.5 l/day is known, Equation 7 can be used to predict more accurately the expected change in serum $[\text{Na}^+]$; the patient's serum $[\text{Na}^+]$ would decrease by 13.7 mEq/l in response to infusion of 1 l of normal saline supplemented with 40 mEq K^+ . Equation 7 can also be used to calculate the desired volume and rate of fluid replacement. If an increase in serum $[\text{Na}^+]$ of 0.5 mEq/l/h or 12 mEq/day is desired, one would need to infuse 16.4 l of normal saline with 40 mEq/l of K^+ or, alternatively, 2.8 l of 3% saline over 24 h. If one wishes to correct the hyponatraemia more conservatively to a maximum of 8 mEq/l/day, as recommended by Oh *et al.* [11], one would need to infuse 13.3 l of normal saline with 40 mEq potassium chloride over the 24 h period.

Equation 7 can also be adjusted to account for any significant extrarenal losses as follows:

$$\Delta \text{Serum } [\text{Na}^+] = \{(V_i)[\text{Na}^+ + \text{K}^+]_{\text{inf}} - (V_u)[\text{Na}^+ + \text{K}^+]_u - (V_o)[\text{Na}^+ + \text{K}^+]_o - (\Delta V)[\text{Na}^+]_s\} / [\text{TBW} + (\Delta V)] \quad (9)$$

where $[\text{Na}^+ + \text{K}^+]_o$ are the Na^+ and K^+ concentrations in extrarenal fluid losses, V_o is the volume of extrarenal fluid losses, and $\Delta V = V_i - (V_u + V_o)$.

Not wanting to oversimplify things, none of the proposed formulas will provide an exact estimate of changes in serum $[\text{Na}^+]$ following the infusion of an i.v. solution, since the initiation of treatment itself will result in changes in urine volume and electrolyte composition. Thus, most importantly, one must frequently reassess the status of a dysnatraemic patient and adjust fluid management appropriately. Importantly, the same formula can be used for both hypo- and hypernatraemic patients regardless of whether they are volume depleted, euvolaemic or hypervolaemic.

To demonstrate further the necessity of accounting for extrarenal water and electrolyte losses in cases where such losses are significant, we will present an additional case in which estimated changes in serum $[\text{Na}^+]$ are calculated using Equations 7, 8 and 9, and then compared with Equation 5.

Case 2

A 45-year-old male weighing 70 kg with inflammatory bowel disease and multiple bowel resections with a colostomy was admitted to the hospital with nausea, vomiting, and an increase in his ostomy output to 3 l/day for the preceding 3 days. Physical examination revealed a cachectic male in moderate distress. Vital statistics were: temperature 36.9°C; BP 80/50 mmHg with orthostatic changes, HR 110 beats/min; and RR 22 breaths/min. His examination was otherwise remarkable for mild lethargy, dry mucous membranes and flat jugular neck veins. Abdominal examination showed diffuse tenderness to palpation but no rebound or guarding, and normal bowel sounds were present. Laboratory data and fluid prescriptions based on Equations 5, 7, 8 and 9 are shown in Table 1.

Discussion

This case demonstrates the importance of accounting for extrarenal losses of electrolytes in estimating the changes in $[\text{Na}^+]_s$ for a given fluid prescription when such losses are significant. Case 2 was a patient with hypovolaemic hyponatraemia secondary to volume depletion from excessive gastrointestinal losses *via* his ostomy. Calculations based on Equation 5 greatly underestimate the impact of 1 l of normal saline on the

change in $[Na^+]_s$ since they do not account for continued urinary and gastrointestinal electrolyte and water losses. Thus, based on Equation 5, more than five times the amount of normal saline needed for appropriate correction of his serum $[Na^+]$ would be administered, which would raise the serum $[Na^+]$ too rapidly, possibly resulting in serious sequelae.

Renal and extrarenal fluid and electrolyte losses can greatly influence the response to therapy in both hypo- and hypernatraemic states. Failure to account for these losses using the currently available formulas can lead to a delay in correction or even worsening of the dysnatraemia in certain cases. The formulas we have presented can be modified to account for all fluid and electrolyte losses, and can estimate the change in $[Na^+]_s$ in response to any volume and composition of infused fluids. The versatility of Equation 8 allows for simplification or expansion as needed and can also be useful, under certain circumstances, in estimating the electrolyte composition of any body fluid if the direct laboratory measurements are not available.

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Appendix

The input formula

Adrogué and Madias mathematically derived their novel formula as follows [8].

Since Na^+ salts comprise the main extracellular osmoles, and the two major body fluid compartments

(extracellular and intracellular) are in osmotic equilibrium, the total body osmoles can be conveniently estimated as:

$$\text{Total body osmoles} \approx (2 \times [Na^+]_s) \times TBW$$

Similarly:

$$\begin{aligned} \text{Osmolar content of 1 l of infused fluid} \\ = (2 \times [Na^+]_i) \times 1 \text{ l} \end{aligned}$$

Since the calculations of Adrogué and Madias focused on the changes in $[Na^+]$ only, they ignored the osmolar contribution from anions in all calculations. Thus:

$$\text{Total body cation osmoles (TBCO)} = [Na^+]_s \times TBW$$

Similarly:

$$\begin{aligned} \text{Infusate cation osmoles per litre of} \\ \text{infused fluid (ICO)} = \text{infusate } Na^+ = [Na^+]_{inf} \times 1 \text{ l} \end{aligned}$$

which makes the total body cation osmoles after infusion of 1 l (TBICO) equal to TBCO + ICO.

Since Na^+ is expressed in serum as a concentration (mEq/l), in order to estimate the final $[Na^+]_F$ ($[Na^+]_F$), TBICO is divided by $TBW + 1 \text{ l}$ from infusate:

$$[Na^+]_F = \text{TBCO} / (TBW + 1 \text{ l})$$

or

$$[Na^+]_F = (\text{TBCO} + \text{ICO}) / (TBW + 1 \text{ l})$$

Substituting the terms:

$$[Na^+]_F = \{([Na^+]_s \times TBW) + ([Na^+]_{inf} \times 1 \text{ l})\} / (TBW + 1 \text{ l})$$

Since the change in serum $[Na^+]$ ($\Delta \text{Serum } [Na^+]$) is the difference between $[Na^+]_F$ and the initial $[Na^+]_s$:

$$\Delta \text{Serum } [Na^+] = [Na^+]_F - [Na^+]_s$$

If we substitute for $[Na^+]_F$:

$$\begin{aligned} \Delta \text{Serum } [Na^+] = \{ & ([Na^+]_s \times TBW) \\ & + ([Na^+]_{inf} \times 1 \text{ l}) / \\ & (TBW + 1 \text{ l}) \} - [Na^+]_s \end{aligned}$$

Using a common denominator:

$$\begin{aligned} \Delta \text{Serum } [Na^+] = & [(Na^+]_s \times TBW) + ([Na^+]_{inf} \times 1 \text{ l}) \\ & - [Na^+]_s (TBW + 1 \text{ l}) / (TBW + 1 \text{ l}) \end{aligned}$$

Simplifying the formula:

$$\begin{aligned} \Delta \text{Serum } [Na^+] = & [(Na^+]_{inf} \times 1 \text{ l}) \\ & - ([Na^+]_s \times 1 \text{ l}) / (TBW + 1 \text{ l}) \end{aligned}$$

Ignoring the 1 l in the calculation, we are left with:

$$\Delta \text{Serum } [\text{Na}^+] = ([\text{Na}^+]_{\text{inf}} - [\text{Na}^+]_{\text{s}}) / (\text{TBW} + 1 \text{ l})$$

Because of the cation contribution of K^+ , the revised formula becomes:

$$\Delta \text{Serum } [\text{Na}^+] = ([\text{Na}^+ + \text{K}^+]_{\text{inf}} - [\text{Na}^+]_{\text{s}}) / (\text{TBW} + 1 \text{ l})$$

In order to adjust for changes based on $>1 \text{ l}$ infusate, the formula is multiplied by the volume of infusate (V_i):

$$\Delta \text{Serum } [\text{Na}^+] = V_i ([\text{Na}^+ + \text{K}^+]_{\text{inf}} - [\text{Na}^+]_{\text{s}}) / (\text{TBW} + 1 \text{ l}) \quad (\text{A})$$

The output formula:

$$\text{Total body cation osmoles (TBCO)} = [\text{Na}^+]_{\text{s}} \times \text{TBW}$$

Similarly:

$$\text{Urinary cation osmoles per litre of urinary output (UCO)} = \text{urinary } \text{Na}^+ = [\text{Na}^+]_{\text{u}} \times 1 \text{ l}$$

which makes the TBCO after 1 l urine output (TBUCO) = TBCO - UCO.

Since serum Na^+ is expressed as a concentration (mEq/l), in order to estimate $[\text{Na}^+]_{\text{F}}$:

$$[\text{Na}^+]_{\text{F}} = \text{TBUCO} / (\text{TBW} - 1 \text{ l})$$

or

$$[\text{Na}^+]_{\text{F}} = (\text{TBCO} - \text{UCO}) / (\text{TBW} - 1 \text{ l})$$

Substituting the terms:

$$[\text{Na}^+]_{\text{F}} = \{([\text{Na}^+]_{\text{s}} \times \text{TBW}) - ([\text{Na}^+]_{\text{u}} \times 1 \text{ l})\} / (\text{TBW} - 1 \text{ l})$$

The change in serum $[\text{Na}^+]$ is the difference between $[\text{Na}^+]_{\text{F}}$ and $[\text{Na}^+]_{\text{s}}$:

$$\Delta \text{Serum } [\text{Na}^+] = [\text{Na}^+]_{\text{F}} - [\text{Na}^+]_{\text{s}}$$

Substituting the appropriate terms for $[\text{Na}^+]_{\text{F}}$:

$$\Delta \text{Serum } [\text{Na}^+] = \{([\text{Na}^+]_{\text{s}} \times \text{TBW}) - ([\text{Na}^+]_{\text{u}} \times 1 \text{ l})\} / (\text{TBW} - 1 \text{ l}) - [\text{Na}^+]_{\text{s}}$$

Rearranging the formula and using a common denominator:

$$\Delta \text{Serum } [\text{Na}^+] = \{([\text{Na}^+]_{\text{s}} \times \text{TBW}) - ([\text{Na}^+]_{\text{u}} \times 1 \text{ l}) - [[\text{Na}^+]_{\text{s}} (\text{TBW} - 1 \text{ l})]\} / (\text{TBW} - 1 \text{ l})$$

Rearranging the numerator:

$$\Delta \text{Serum } [\text{Na}^+] = \{([\text{Na}^+]_{\text{s}} \times \text{TBW}) - ([\text{Na}^+]_{\text{u}} \times 1 \text{ l}) - ([\text{Na}^+]_{\text{s}} \times \text{TBW}) + ([\text{Na}^+]_{\text{s}} \times 1 \text{ l})\} / (\text{TBW} - 1 \text{ l})$$

Since the term $[\text{Na}^+]_{\text{s}} \times \text{TBW}$ exists in positive and negative forms, they cancel each other out and the formula simplifies to:

$$\Delta \text{Serum } [\text{Na}^+] = - \{([\text{Na}^+]_{\text{u}} \times 1 \text{ l}) + ([\text{Na}^+]_{\text{s}} \times 1 \text{ l})\} / (\text{TBW} - 1 \text{ l})$$

Ignoring the 1 l in the calculation and rearranging the numerator:

$$\Delta \text{Serum } [\text{Na}^+] = ([\text{Na}^+]_{\text{s}} - [\text{Na}^+]_{\text{u}}) / (\text{TBW} - 1 \text{ l})$$

Multiplying this formula by the urine output (V_u) in 1/24 h will provide the change in serum $[\text{Na}^+]$ based on urinary losses over the 24 h in question.

The final formula becomes:

$$\Delta \text{Serum } [\text{Na}^+] = [V_u ([\text{Na}^+]_{\text{s}} - [\text{Na}^+]_{\text{u}})] / (\text{TBW} - 1 \text{ l})$$

Factoring in the contribution of K^+ :

$$\Delta \text{Serum } [\text{Na}^+] = [V_u ([\text{Na}^+]_{\text{s}} - [\text{Na}^+ + \text{K}^+]_{\text{u}})] / (\text{TBW} - 1 \text{ l}) \quad (\text{B})$$

Based on the above calculations, one would expect the net change in serum $[\text{Na}^+]$ for a given input and output to simply be the sum of formulas A and B; however, this is not the case. The net change in serum $[\text{Na}^+]$ when one considers both input and output together depends on the net change in TBW resulting from input and output volumes. One cannot simply add formulas A and B and use the denominators $\text{TBW} + 1$ and $\text{TBW} - 1$, respectively; the denominator for both input and output formulas becomes the same when considering input and output together. Therefore one must divide the sum of the numerators of formulas A and B by the final TBW, which is the sum of the initial TBW and the ΔTBW , the latter being the difference between input and output volumes.

$$\Delta \text{Serum } [\text{Na}^+] = \{[\text{Na}^+]_{\text{inf}} (V_i) - [\text{Na}^+]_{\text{s}} (V_i - V_u) - [\text{Na}^+]_{\text{u}} (V_u)\} / [\text{TBW} + (V_i - V_u)]$$

Based on 1 l of infusate and 1 l of output the formula reduces to:

$$\Delta \text{Serum } [\text{Na}^+] = ([\text{Na}^+]_{\text{inf}} - [\text{Na}^+]_{\text{u}}) / \text{TBW}$$

If the patient is aneuric then the formula reduces to:

$$\Delta \text{Serum } [\text{Na}^+] = [V_i ([\text{Na}^+]_{\text{inf}} - [\text{Na}^+]_{\text{s}})] / [\text{TBW} + (V_i)]$$

which is the original formula introduced by Adrogue and Madias.