Treatment of severe chronic hypotonic hyponatremia: a new treatment model

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ABSTRACT

Recommended treatment of severe hypotonic hyponatremia is based on the infusion of 3% sodium chloride solution, with a daily correction rate below 10 mEq/L of sodium concentration, according to the Adrogué and Madias formula that includes the current desired change in sodium concentrations. However, such treatment needs close monitoring of the rate of infusion and does not take into account the body weight or age of the patient. This may result in hypercorrection and neurological damage. We made an inverse calculation using the same algorithms of the Adrogué and Madias formula to estimate the number of vials of sodium chloride needed to reach a correction rate of the serum sodium concentration below 0.4 mEq/h, taking into account the body weight and age of the patient. Three tables have been produced, each containing the number of vials to be infused, according to the patient's age and body weight, the serum sodium concentration, and the rate of correction over 24 h to avoid the risk of brain damage. We propose a new practical model to calculate the need of sodium chloride infusate to safely correct the hyponatremia. The tables make treatment easier to manage in daily clinical practice in a wide range of patient ages and body weights.

Introduction

Hyponatremia, defined as serum sodium concentration less than 136 mEq/L, is the most frequent eletrolytic disorder and is found in approximately one-third of hospitalized patients.[1] Total sodium content is approximately 3000 mEq, while sodium content in a liter of plasma, *i.e.* natremia, is 135-145 mEq/L. Variations in natremia may be the consequence of variations in sodium content and/or water in the organism. Mild natremia is 135-130 mEq/L, moderate 129-120, severe less than 120 mEq/L. According to the duration, acute forms present within 48 h, chronic forms are those presented after 48 h. Mild and moderate forms are usually asymptomatic. However, when concentrations of sodium are very low, neurological symptoms may appear, such as cephalea, lethargy, muscular weakness, temporal-spatial disorientation, psychosis, convulsions or even coma, respiratory depression and sometimes death.[2,3]

In conditions of plasma hypotonicity, the nerve cell may undergo irreversible damage because an acute reduction in the concentration of sodium in the blood to 125 mEq/L provokes a passage of water from the plasma to the intracellular compartment. This results in cellular swelling and cerebral edema. If the same value of natremia is reached slowly, *i.e.* over 1-2 days, the cells can adapt to the change and re-establish a balance by losing solutes (potassium, glutamates and thiamine) and the consequent leaking of water from within the cell to the cephalorachidian liquid and to the blood.

Severe chronic hypotonic hyponatremia is a clinical condition characterized by plasma hypotonia and by a concentration of sodium less than 120 mEq/L following both renal and extrarenal loss of sodium for over 48 h.[4] Severe chronic hyponatremia often does not have obvious symptoms because our organism is capable of activating efficient compensation mechanisms. Recognition of the condition is, however, important because it is associated to higher mortality rates, but also because correction of the condition is an extremely delicate procedure. Inappropriate therapy can cause damage. In fact, a rapid correction of the natremia of over 0.5 mEq/h can cause neurological changes, of which the most serious is osmotic demyelination syndrome (pontine and extrapontine myelinolisis).[5]

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Current treatment of severe chronic hypotonic hyponatremia involves use of a 3% hypertonic saline solution in a 24-h period calculating the resultant change in sodium concentration with the Adrogué and Madias formula.[6] The aim is to achieve a correction of natremia of less than 10 mEq/L in a 24-h period and not more than 18 mEq/L over 48 h.[7]

This paper aims to demonstrate that the treatment currently used, above all in patients with a low body weight, requires careful monitoring with frequent correction of the infusion velocity to avoid dangerous hypercorrection over the recommended 0.4 mEq/h limit. We propose a therapeutic schedule to be integrated into the current model that considers the initial natremia and also incorporates parameters of patient age and body weight using easy-to-read tables. The minimum objective is to achieve over 24 h natremia that does not exceed 10 mEq; this corresponds to an hourly correction of 0.4 mEq thus avoiding dangerous hypercorrection.[8]

Current treatment of severe chronic hypotonic hyponatremia

In chronic forms, correction of natremia must be gradual because the organism has already activated compensation mechanisms.[9] In clinical practice, the Adrogué and Madias formula to calculate the variation in natremia, starting treatment with a 3% hypertonic saline solution, 1 L of which contains 523 mEq of sodium. In the following examples, we have considered treatment with a 3% hypertonic saline solution, containing 523 mEq/L because the preconstituted 3% solution containing 512 mEq/L is not readily available on the market. The hypertonic solution used in our example is made up by taking 200 mL of solution from a liter of physiological solution and adding 20 vials of 10 mL NaCl to the remaining 800 mL; each vial contains 20 mEq of Na.

Adrogué and Madias formula:

$$\text{variation in sodium}=\frac{\text{infused sodium-actual sodium}}{\text{body water+infused water}}$$

The estimated total body water, expressed in liters, is calculated as a fraction of body weight and varies with age. It corresponds to 60% and 50%, respectively, in men and women under 65 years of age and to 50% and 45%, respectively, in men and women over 65 years of age.

The following examples show that severe chronic hypotonic hyponatremia can not always be treated with 3% saline solution unless the infusion is carefully monitored given the risk of dangerous hypercorrection during the 24-h period, particularly in patients with a low body weight.

Example 1

A 40-year old male, weighing 70 kg with 110 mEq/L natremia.

Using a 3% hypertonic saline solution, in a 24-h period, a 9.60 mEq/L variation in sodium concentration can be achieved.

$$\text{Variation in sodium concentration}=\frac{523-110}{42+1}=9.60\text{ mEq/L}$$

If the same procedure is used in patients with a different weight, age and/or natremia, there may be a hypercorrection of the sodium concentration.

Example 2

A 40-year old man, weighing 50 kg with a 110 mEq/L natremia.

$$\text{Variation in sodium concentration}=\frac{523-110}{30+1}=13.3\text{ mEq/L}$$

Example 3

A 70-year old man, weighing 60 kg with 110 mEq/L natremia.

$$\text{Variation in sodium concentration}=\frac{523-110}{30+1}=13.3\text{ mEq/L}$$

Example 4

A 72-year old woman, weighing 68 kg with 110 mEq/L natremia.

$$\text{Variation in sodium concentration}=\frac{523-110}{30.6+1}=13.06\text{ mEq/L}$$

Example 5

A 73-year old woman, weighing 51 kg with 115 mEq/L natremia.

$$\text{Variation in sodium concentration}=\frac{523-115}{22.95+1}=17.03\text{ mEq/L}$$

Example 6

A 65-year old woman, weighing 52 kg with 116 mEq/L natremia.

$$\text{Variation in sodium concentration}=\frac{523-118}{23.4+1}=16.5\text{ mEq/L}$$

Example 7

A 75-year old man, weighing 50 kg with 118 mEq/L natremia.

$$\text{Variation in sodium concentration}=\frac{523\text{-}118}{30+1}= 13.06\ \text{mEq/L}$$

The examples described above show that in many patients, with different weight, age and/or natremia, treatment with 3% hypertronic saline solution can result in dangerous hypercorrection if not carefully monitored. Furthermore, in examples 5-7 (see above), for any natremia value below 125 mEq/L, in patients who weigh less than 53 kg, there was always hypercorrection. This shows that the current therapeutic approach cannot be adopted in all patients and never in patients who weigh less than 53 kg. Instead, therapy must be personalized for each patient and carefully monitored.

In order to avoid hypercorrection of natremia with 3% hypertonic saline solution in a 24-h period, even in the cases described above, the velocity of infusion must be varied and natremia must be checked every 2-3 h.

Materials and Methods

We used the Adrogué and Madias formula to calculate the number of vials of 3% sodium chloride to be infused in order to safely restore natremia levels in cases of hyponatremia. Treatment of severe chronic hypotonic hyponatremia is based on infusion of a 3% hypertonic saline solution at an infusion velocity calculated according to the Adrogué and Madias formula:

$$\text{variation in sodium concentration}=\frac{\text{infused Na-initial Na}}{\text{infused water+body water}}$$

This calculates the variation in natremia achieved with infusion of 3% hypertonic solution.

For example, for a 55-year old man weighing 60 kg with natremia of 110 mEq/L, substituting the data of the formula results in:

$$\text{variation in sodium concentration}=\frac{523\text{-}110}{32+1}= 413/33 = 12.51\ \text{mEq/L}$$

where
523 is the infused Na contained in 1 L of 3% hypertonic solution;
110 is the initial natremia;
1 is the water infused with 1 L of hypertonic solution;
32 is the body water calculated as 60% of body weight.

Body water is calculated according to age, gender and body weight as follows: in men and women under 65 years of age, body water corresponds to 60% and 50% of body weight, respectively. In those over 65 years of age, the corresponding values are 50% and 45%, respectively. To calculate the variation in natremia, we need to calculate how long infusion lasts in order to obtain the correct hourly natremia velocity; this should not exceed 0.4 mEq/h, as follows:

$$\text{duration of infusion}=\text{variation in Na concentration}/0.4=32\ \text{h}$$

Therefore, in this case, infusion should last 32 h and infusion velocity should be calculated as:

$$\text{infusion velocity}=1000\ \text{mL}/32\ \text{h}=31.25\ \text{mL/h}$$

This means that at the end of a 32-h period of infusion, a variation in natremia of 12.5 mEq is achieved and, therefore, a natremia of 110+12.5=122.5 mEq/L is obtained.

The Adrogué and Madias formula can be used to calculate the number of vials of NaCL to add to 1 L of 0.9% physiological solution to obtain a variation in sodium concentration that does not exceed 10 mEq in a 24-h period.

In our example, we can calculate:

$$\text{variation in sodium concentration}=\frac{\text{infused sodium-initial sodium}}{\text{infused water+body water}}$$

The known values according to the formula can be replaced:

$$10=\times\text{-}110/(1+32)$$

where
10 is the variation in sodium;
× is the unknown amount of sodium infused;
110 is initial sodium;
1 is water infused;
32 is body water.

We can consider the unknown amount of infused sodium (×) separately:

$$\times=10(1+32)+110;\ \times=330+110=440\ \text{mEq/L};$$

This calculated the mEq to be added to 1 L of 0.9% physiological solution to obtain a variation in 10 mEq/24 h: 440 mEq/L. But 1 L of physiological solution contains 154 mEq of Na and so the number of vials of NaCl to be added will be:

$$440\ \text{mEq-}154\ \text{mEq}=286\ \text{mEq/L}$$

Each vial of NaCl contains 20 mEq/10 mL. Therefore, to calculate the number of vials to be infused the result must be divided by 20:

no. of vials NaCl=286:20=14.3

Therefore, in our case, treatment should consist of an infusion of 1 L of 0.9% physiological solution with the addition of 14 vials of NaCl infused at a velocity of (1000:24=41) 41 mL/h.

On completion of the infusion, a variation in sodium concentration of 10 mEq/24 h is obtained and 110+10=120 mEq/L natremia is achieved.

Sodium to be infused=target variation in sodium (water infused+body water)+initial sodium.

One liter of 0.9% physiological solution contains 154 mEq of Na and this must be subtracted from the formula as follows:

sodium to be infused=target variation in sodium concentration (water infused+body water)+ initial sodium value-154

If we divide the total by 20 we obtain the number of vials of NaCl to be added to the physiological solution and, therefore, the final formula will be:

no. of vials of NaCl to be infused= target variation in Na concentration (water infused+body water)+initial Na-154/20.

Infusion velocity can always be set at 41 mL/h.

Results

Three tables have been formulated to correct natremia (Tables 1-3) by inverting the calculation of the parameters set out in the Adroguè and Madias formula. Each Table shows the number of vials of sodium chloride to add to 0.9% physiological solution on the basis of patient natremia, body weight, age and gender, and the target natremia to be achieved to avoid hypercorrection.

The first objective is, where possible, to achieve natremia values of more than 125 mEq/L in a 24-h period.

The target natremia value must not exceed the recommended safety levels of 0.4 mEq/H and 10 mEq/24 h.

Any hourly or 24-h variation in sodium concentra-

Table 1. Hyponatremia correction in women over 65 years of age.

	No. vials of NaCl 20 mEq/10 mL to be added to 1L of physiological solution										
Initial natremia (mEq/L)	**50 kg**	**55 kg**	**60 kg**	**65 kg**	**70 kg**	**75 kg**	**80 kg**	**85 kg**	**90 kg**	**95 kg**	**100 kg**	**Natremia achieved in 24 h**
110	9.5	10.5	11.5	13	14	15	16	17.5	18.5	19.5	20.5	121-122
111	9.5	10.5	11.5	13	14	15	16	17.5	18.5	19.5	20.5	120-121
112	9.5	10.5	12	13	14	15	16	17.5	18.5	19.5	21	121-122
113	9.5	10.5	12	13	14	15	16.5	17.5	18.5	19.5	21	122-123
114	9.5	10.5	12	13	14	15	16.5	17.5	18.5	19.5	21	124-125
115	9.5	11	12	13	14	15.5	16.5	17.5	18.5	20	21	124-125
116	9.5	11	12	13	14	15.5	16.5	17.5	18.5	20	21	125-126
117	10	11	12	13	14.5	15.5	16.5	17.5	19	20	21	126-127
118	10	11	12	13	14.5	15.5	16.5	17.5	19	20	21	127-128
119	10	11	12	13	14.5	15.5	16.5	17.5	19	20	21	128-129
120	10	11	12	13	14.5	15.5	16.5	18	19	20	21	129-130
121	10	11	12	13.5	14.5	15.5	16.5	18	19	20	21	130-131
122	10	11	12.5	13.5	14.5	15.5	17	18	19	20	21.5	131-132
123	10	11	12.5	13.5	14.5	15.5	17	18	19	20	21.5	132-133
124	10	11	12.5	13.5	14.5	15.5	17	18	19	20	21.5	133-134

Body water calculated as 45% of body weight. No. vials of Na for infusion=[(H_2O body water+H_2O infused)×(target Na-initial Na)+initial Na-154]/20.

Table 2. Hyponatremia correction in women under 65 and men over 65 years of age.

Initial natremia (mEq/L)	No. vials of NaCl 20 mEq/10 mL to be added to 1L of physiological solution											Natremia achieved in 24 h
	50 kg	55 kg	60 kg	65 kg	70 kg	75 kg	80 kg	85 kg	90 kg	95 kg	100 kg	
110	10.5	12	13	14.5	15.5	17	18	19.5	20.5	22	23	119-120
111	10.5	12	13	14.5	15.5	17	18	19.5	20.5	22	23	120-121
112	11	12	13	14.5	16	17	18	19.5	21	22	23	121-122
113	11	12	13.5	14.5	16	17	18.5	19.5	21	22	23.5	122-123
114	11	12	13.5	14.5	16	17	18.5	19.5	21	22	23.5	123-124
115	11	12	13.5	14.5	16	17	18.5	19.5	21	22	23.5	124-125
116	11	12	13.5	14.5	16	17	18.5	19.5	21	22	23.5	125-126
117	11	12.5	13.5	15	16	17	18.5	20	21	22	23.5	126-127
118	11	12.5	13.5	15	16	17.5	18.5	20	21	22.5	23.5	127-128
119	11	12.5	13.5	15	16	17.5	18.5	20	21	22.5	23.5	128-129
120	11	12.5	13.5	15	16	17.5	18.5	20	21	22.5	23.5	129-130
121	11	12.5	13.5	15	16	17.5	18.5	20	21	22.5	23.5	130-131
122	11	12.5	14	15	16	17.5	19	20	21	22.5	24	131-132
123	11.5	12.5	14	15	16.5	17.5	19	20	21.5	22.5	24	132-133
124	11.5	12.5	14	15	16.5	17.5	19	20	21.5	22.5	24	133-134

Body water calculated as 50% of body weight. No. vials of Na for infusion=[(H_2O body water+H_2O infused)×(target Na-initial Na)+initial Na-154]/20.

Table 3. Hyponatremia correction in men under 65 years of age.

Initial natremia (mEq/L)	No. vials of NaCl 20 mEq/10 mL to be added to 1L of physiological solution											Natremia achieved in 24 h
	50 kg	55 kg	60 kg	65 kg	70 kg	75 kg	80 kg	85 kg	90 kg	95 kg	100 kg	
110	13	14.5	16	17.5	19	20.5	22	23.5	25	26.5	28	119-120
111	13	14.5	16	17.5	19	20.5	22	23.5	25	26.5	28	121-122
112	13	15	16	18	19	21	22	24	25	27	28	121-122
113	13.5	15	16.5	18	19.5	21	22.5	24	25.5	27	28.5	122-123
114	13.5	15	16.5	18	19.5	21	22.5	24	25.5	27	28.5	123-124
115	13.5	15	16.5	18	19.5	21	22.5	24	25.5	27	28.5	124-125
116	13.5	15	16.5	18	19.5	21	22.5	24	25.5	27	28.5	125-126
117	13.5	15	16.5	18	19.5	21	22.5	24	25.5	27	28.5	126-127
118	13.5	15	16.5	18	19.5	21	22.5	24	25.5	27	28.5	127-128
119	13.5	15	16.5	18	19.5	21	22.5	24	25.5	27	28.5	128-129
120	13.5	15	16.5	18	19.5	21	22.5	24	25.5	27	28.5	129-130
121	13.5	15	16.5	18	19.5	21	22.5	24	25.5	27	28.5	130-131
122	14	15	17	18	20	21	23	24	26	27	29	131-132
123	14	15.5	17	18.5	20	21.5	23	24.5	26	27.5	29	132-133
124	14	15.5	17	18.5	20	21.5	23	24.5	26	27.5	29	133-134

Body water calculated as 60% of body weight. No. vials of Na for infusion=[(H_2O body water+H_2O infused)×(target Na-initial Na)+initial Na-154]/20.

tions can be achieved by a simple variation in the value of the formula specified in each Table under *target sodium*.

Conclusions

Our organism can manage and maintain well-balanced basal acid, hydroelectrolyte, osmotic and volemic levels. In pathological conditions, the therapeutic strategies adopted are sometimes inadequate and can result in a sudden change in the delicate balance between these levels causing damage that can sometimes be irreversible.

One obvious example is the current treatment of severe chronic hypotronic hyponatremia that consists in infusion of 3% hypertonic saline solution. In some patients, such treatment corrects the natremia too quickly and can be responsible for serious side effects. The velocity per hour to correct natremia must not exceed 0.4 mEq/L/h and must be over 18 mEq/L/48 h.[10] In patients suffering from malnutrition, with advanced phase hepatic pathologies, there is a higher susceptibility to pontine myelinolysis and, therefore, a slower velocity of infusion must be used to correct the natremia.[11]

In our clinical practice, and above all in patients with low body weight, use of the Adrogué and Madias formula requires a variety of variations in infusion velocity of the 3% hypertonic solution to avoid dangerous hypercorrection. We have, therefore, formulated some tables for correcting severe chronic hypotonic hyponatremia that take into consideration hourly velocity of correction, weight, age and gender of the patient, and the initial natremia value.[12] The tables can be used in all cases of severe chronic hypotonic hyponatremia that require infusion of sodium. The advantages of our proposal over the current therapy using 3% hypertonic solution are: i) to avoid dangerous hypercorrection of natremia in a 24-h period; ii) to help monitor therapy and avoids calculation errors; iii) to offer a diversified treatment according to initial natremia values, and patient age and weight; iv) most importantly, to achieve an hourly correction of natremia that does not exceed 0.4 mEq/h. This is the recommended safety limit above which significant symptoms are rarely presented.

Our proposed treatment should not be considered as a substitute to current therapy but should rather be integrated into it. Use of these tables in daily clinical practice could help monitor therapy and avoid the frequent variations in infusion velocity. This means a less stressful approach to disease management also for those physicians who are not expert in hydroelectrolyte problems.

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