Witness Statement Ref. No. 342/1

NAME OF CHILD: Lucy Crawford (Rachel Ferguson Governance)

Name: Ian S.Young

Title: Professor

Present position and institution:

Professor of Medicine, Queen's University Belfast

Consultant in Clinical Biochemistry, Belfast Health and Social Care Trust

Previous position and institution:
[As at the time of the child's death]

Membership of Advisory Panels and Committees:
[Identify by date and title all of those between January 1995-December 2004]

Previous Statements, Depositions and Reports:
[Identify by date and title all those made in relation to the child's death]

096-007-039 Statement to the PSNI

091-010-060 4/5/2006 Deposition to the Coroner

WS-178-1 - Inquiry Witness Statement (PDF 1.8MB)

WS-178-2 - Supplemental Inquiry Witness Statement (PDF 9MB)

WS-178-3 - Supplemental Inquiry Witness Statement (PDF 1.7MB)

WS-178-5 - Supplemental Inquiry Witness Statement (PDF 10MB)

OFFICIAL USE: List of previous statement, depositions and reports attached:		
Ref:	**Date:**	

Other points you wish to make including additions to any previous Statements, Depositions and or Reports
[Please attach additional sheets if more space is required]

THIS STATEMENT IS TRUE TO THE BEST OF MY KNOWLEDGE AND BELIEF

Signed: Ian Young **Ian Young** **Dated: 17/6/13** 19/6/13

I have been asked by the Inquiry to address the following issues in relation to the likely impact of the administration of normal saline on her serum sodium concentration prior to the collection of a sample which gave a result of 127 mmol/l at approximately 3.30 AM on the morning of 13th April 2000.

(i) the approach being advocated to calculate the likely effect on Lucy's serum sodium level of her having been administered a quantity of normal saline prior to the measurement of 127mmol/l and, in particular, whether it would be likely to have raised it from a level significantly lower than the measured 127mmol/l

(ii) the calculation that approach produces, together with any assumptions made

(iii) a copy of any of the literature (eg extracts from text books or published papers) relied upon in support of the approach taken and the calculation produced

(iv) the exercise should be calculated by reference to the position in 2000, indicating if matters would be different now, the nature of the difference and the reason for it.

I will first address points (i) – (iii) together, and will then comment on how the position has changed as a consequence of further publications after 2000.

a) The position in 2000 and the appropriate calculation at that time:

In 1997 Adrogue and Madias proposed a novel approach and simple calculation to estimate the effect of infusing 1L of a fluid of known sodium concentration of a patient's sodium concentration (Aiding fluid prescription for the dysnatremias - Intensive Care Medicine 1997;23:309-316). This has subsequently become known as the Adrogue-Madias formula. The derivation of the formula, which is given below, is outlined in the paper:

$$\Delta[Na^+]_s = \frac{[Na^+]_{inf} - [Na^+]_s}{TBW + 1}$$

Where: $\Delta[Na^+]_s$ = change in the patient's serum sodium; $[Na^+]_{inf}$ = sodium concentration of the infused fluid; $[Na^+]_s$ = patient's initial serum sodium concentration; TBW = total body water in L.

The 1997 paper provides several illustrations of how the formula can be used to estimate the effect of infusing 1L of various fluids to different patients with hyponatraemia. The authors draw attention to a number of limitations of the proposed equation. It considers the patient as a closed system that incurs no gain or loss of water and electrolytes other than the administered fluid during the time frame of the infusion. In addition, the use of the formula requires an estimate of the patient's total body water content, which will be an approximation.

At the time of Lucy's death in 2000 the application of this formula was the best available approach to estimating the effect of infusion of fluid on a patient's sodium concentration, as indicated by its recommendation in the May 2000 review of Hyponatraemia in the New England Journal of Medicine (Adrogue N Engl J Med 2000; 342:1581-1589). Lucy received 0.9% saline over a short period prior to sample collection and it is likely that there was little loss of water or electrolytes during this short period, and that the assumption of a closed system is not a significant limitation.

The formula can be applied to estimate the effect of infusion of 1L of 0.9% saline on Lucy's serum sodium concentration in the following way:

a) $$\Delta[Na^+]_s = \frac{[Na^+]_{inf} - [Na^+]_s}{TBW + 1}$$

$\Delta[Na^+]_s$ (change in Lucy's sodium) = 127 – $[Na]_s$, where $[Na]_s$ is Lucy's sodium prior to the administration of the 0.9% saline

$[Na^+]_{inf}$ = sodium concentration of the infused fluid, which is 154 mmol/L

$[Na^+]_s$ = Lucy's sodium prior to the administration (which we wish to calculate)

TBW = total body water in L. This needs to be estimated, since the information required to calculate this is not available to me. I have used a value of 5L for the purposes of the calculation below. The Inquiry's experts may wish to use a different value, but this will not greatly impact on the calculation.

It follows that:

$$b)\quad 127 - [Na^+]_s = \frac{154 - [Na^+]_s}{5 + 1}$$

Sequentially rearranging the equation gives the following:

$$c)\quad 127 - [Na^+]_s = \frac{154 - [Na^+]_s}{6}$$

$$d)\quad 6\,(127 - [Na^+]_s) = 154 - [Na^+]_s$$

$$e)\quad 127x6 - 6[Na^+]_s = 154 - [Na^+]_s$$

$$f)\quad 762 - 6[Na^+]_s = 154 - [Na^+]_s$$

$$g)\quad 762 = 154 - [Na^+]_s + 6[Na^+]_s$$

$$h)\quad 762 - 154 = 5[Na^+]_s$$

$$i)\quad [Na^+]_s = (762 - 154) / 5$$

$$j)\quad [Na^+]_s = 121.6 \text{ mmol/l}$$

In other words, if Lucy had received 1L of 0.9% saline, this would have raised her serum sodium from a pre-treatment value 122 mmol/L to 127 mmol/L (i.e. by 5 mmol/L).

There is some uncertainty about the volume of 0.9% saline which Lucy received before the sample was collected which gave the result of 127 mmol/L. However, the maximum amount which she could have received appears to have been 500 mls. If this was the case, her sodium would have been raised by approximately 2.7 mmol/L from just over 124 to 127 mmol/L.

124mmol/L is therefore the best estimate of Lucy's minimum serum sodium based on the available data and the state of knowledge in 2000, and it is possible that the actual lowest value was higher than this. For instance, if she had received 250 mls of 0.9% saline rather than 500mls prior to sample collection her sodium would have been raised from just under 126 mmol/l to 127 mmol/l.

b) Subsequent developments and current thinking:

The Adrogue-Madias formula remains the most widely used approach to estimating the impact of infusion of sodium containing fluids on a patient's serum sodium. It is recommended in several hyponatraemia guidelines and is utilised in a number of calculators which are in clinical use. However, since 2000 there has been increasing awareness of the limited accuracy of the formula and more complex alternatives have been suggested.

In 2002 Barsoum and Levine discussed the limitations of the Adrogue-Madias formula discussed above and proposed a revised formula which included a factor to allow for ongoing urinary losses during fluid infusion, and which in addition accounted for the contribution of any potassium which was added to the infused fluid (Nephrol Dial Transplant 2002;17:1176-80). Further formulae were suggested by Nguyen and Kurtz in Clin Exp Nephrol. 2003;7:125-37. All of these formulae require knowledge of urinary electrolyte concentrations and based on the information available to me cannot be applied to Lucy's case.

Several authors have attempted to experimentally validate the accuracy of the Adrogue-Madias and other formulae. Liamis et al. in 2006 (Nephrol Dial transplant 2006;21:1564-69) studied 189 patients who had received various intravenous solutions for the correction of dysnatraemias. There conclusion was that the Adrogue-Madias formula predicted with relative accuracy the changes in serum sodium concentration in almost all patients.

In 2007 Mohmand et al. (Clin J Am Soc Nephrol 2007;2:1110-7) reviewed 62 patients who had received hypertonic saline for hyponatraemia and concluded that the Adrogue-Madias formula underestimated the increase in sodium concentration after hypertonic saline. They did not look at the accuracy of the formula following the administration of 0.9% sodium chloride.

In 2008 Linder et al. (Nephrol Dial Transplant (2008) 23: 3501–3508) tested all of the formulae mention above using data from six hundred and eighty-one patient-days (194 hypernatraemic) in 66 patients. With regard to the Adrogue-Madias formula, they concluded that it tended to overestimate change in serum sodium. However, they did not test the formulae in hyponatraemic patients.

In summary, therefore, recent data have cast some doubt on the accuracy of the Adrogue-Madias formula for estimating the change in serum sodium but to date a better guide or tool is not available.

Intensive Care Med (1997) 23: 309–316

ORIGINAL

H. J. Adrogué
N. E. Madias

Aiding fluid prescription for the dysnatremias

Received: 27. September 1996
Accepted: 13 December 1996

This work was presented at the 29th Annual Meeting of the American Society of Nephrology, 3–6 November, 1996, in New Orleans, Louisiana

H. J. Adrogué
Department of Medicine, Baylor College of Medicine, and Renal Section, Department of Veterans' Affairs Medical Center, Houston, Texas, USA

N. E. Madias (✉)
Department of Medicine, Tufts University School of Medicine, and Division of Nephrology, New England Medical Center, Box 172, 750 Washington St., Boston, MA 02111, USA
FAX: +1 (617) 6361355

Abstract *Objective:* The goal of the present study was to develop a novel approach that facilitates the prescription of fluid therapy in patients with abnormal serum sodium concentration.
Methodology and results: The novel approach is based on a simple equation, derived from established principles on the distribution of sodium in body fluids, that estimates the impact of a unit dose, i. e., 1 l of any infusate on the patient's serum sodium concentration. In accordance with the equation, the expected change in the patient's serum sodium concentration in response to 1 l of any infusate ($\Delta[Na^+]_s$) is obtained by subtracting the sodium concentration of the patient's serum from the sodium concentration of the infusate, each expressed in mEq/l, and dividing the result by the patient's estimated total body water expressed in liters (adding 1 l to account for the volume of the infusate). The amount of the particular infusate to be administered over the course of any given time period can be easily computed by dividing the desired $\Delta[Na^+]_s$ at the end of the period by the calculated $\Delta[Na^+]_s$ effected by 1 l of the infusate. The utility and limitations of the proposed approach are presented.
Conclusions: The novel equation is not a means for formulating therapy. Rather, it provides, simply and expeditiously, quantitative projections that can assist the physician in implementing the selected treatment plan for patients with dysnatremias.

Key words Hyponatremia · Hypernatremia · Sodium concentration · Fluid therapy

Introduction

Dysnatremias, that is abnormalities in the serum sodium concentration, are very common electrolyte disturbances occurring in a wide spectrum of patients, from the relatively asymptomatic to the critically ill. Failure to manage these disorders effectively can contribute importantly to patients' morbidity and mortality. Optimal treatment of the dysnatremias, frequently a challenging task, demands a firm grasp of the relevant pathophysiology, sound clinical judgement and close monitoring of the patient's clinical and laboratory parameters [1–3].

As a time-honored rule, physicians generally employ one of several conventional formulas (Table 1) in guiding the implementation of the selected treatment plan [4, 5]. These formulas are based on sound pathophysiologic principles and, indeed, provide a reasonable framework for gauging therapy. Nonetheless, the utility of these equations is diminished by several factors. First, by estimating the cumulative deficits or surfeits of water and sodium existing at the time of the patient's evaluation (Table 1), these equations engage the practitioner to design a fluid prescription that typically extends over a 2- to 3-day period. Yet, the prevailing water and sodium derangement is frequently not static but evolving,

Table 1 Conventional formulas for managing dysnatremias

Formula # 1. $\text{Water deficit} = \text{TBW} \times \frac{\text{current Na}_s}{140} - 1$

Formula # 2. $\text{Water excess} = \text{TBW} - \text{TBW} \frac{\text{current Na}_s}{140}$

Formula # 3. $\text{Sodium requirement} = \text{TBW} \times (\text{desired } [Na^+]_s - \text{current } [Na^+]_s)$

Table 2 Sodium concentration of the most frequently used intravenous infusates

Infusate	$[Na^+]$, mEq/l
5% dextrose in water	0
0.9% sodium chloride in water	154
Ringer's lactate	130
0.45% sodium chloride in water	77
0.2% sodium chloride in 5% dextrose in water	34
3% sodium chloride in water	513

thus calling for frequent revision of the fluid prescription. Second, the conventional formulas fail to link directly the selected infusate with the projected change in the patient's sodium concentration. For example, a circuitous procedure is needed to translate a given amount of sodium required to raise serum sodium concentration to a desired level, as projected by formula # 3 (Table 1), to an infusion rate of a 3% sodium chloride solution. Third, solutions of different composition are commonly employed in repairing the dysnatremias (Table 2). Therefore, an expeditious projection of the variable impact of these solutions on the dysnatremia at hand would be highly desirable. For example, depending on whether a hypernatremic patient is euvolemic or hypovolemic, repair of the disorder requires the administration of free water (i.e., 5% dextrose in water) or sodium-containing solutions (e.g., normal saline, half-normal saline, or quarter-normal saline), respectively. Yet, currently existing formulas do not provide information on the differential impact of solutions of variable sodium concentration on the patient's hypernatremia.

Given these considerations, we have derived a simple equation that provides an expedient and direct projection of the impact of the unit dose, i.e., 1 l of any infusate on the patient's serum sodium concentration, the projection being expressed in mEq/l. The equation is based on precisely the same principles as conventional formulas (Table 1) and, in fact, represents a mathematical derivation. Consequently, the novel equation does not require experimental validation. We wish to demonstrate the utility of the proposed equation as an ancillary tool for managing both hypernatremia and hyponatremia. We should emphasize strongly at the outset that, as is true for all conventional formulas (Table 1), the proposed equation is not intended to circumvent sound pathophysiologic reasoning, and, therefore, is not a means for formulating therapy. Rather, this equation is presented as an adjunctive tool that can assist the practitioner to implement the selected treatment plan, as formulated by pathophysiologic and clinical considerations. In addition to its utility, the limitations of this approach are examined.

The equation

The expected change in the patient's serum sodium concentration, ($\Delta[Na^+]_s$) as a result of retention of 1 l of any one of the infusates usually administered in fluid therapy can be estimated by the following equation:

$$\Delta[Na^+]_s = \frac{Na_{inf} - Na_s}{TBW + 1}$$

where $[Na^+]_{inf}$ and $[Na^+]_s$ represent the sodium concentration of the infusate and the patient's serum, respectively, expressed in mEq/l, and TBW represents the patient's estimated total body water, expressed in liters. The output of the equation, $\Delta[Na^+]_s$, is expressed in mEq/l. The numerator of the right-hand side of the above equation, $[Na^+]_{inf} - [Na^+]_s$, represents a simplification of the expression ($[Na^+]_{inf}$ – initial $[Na^+]_s$) × 1 l (Appendix, Eq. A-10), thus accounting for the output of the above equation being expressed in mEq/l. As indicated in the Appendix, the equation is based on the physiologic principle that the serum sodium concentration is determined by the total body cationic osmoles and total body water. The impact of the infusion on the serum sodium concentration is then derived by a computation of the resultant changes in total body cationic osmoles and water. The convenient feature of the equation is that it estimates directly, in mEq/l, the anticipated consequence of retaining 1 l of the administered solution on the parameter of concern, the serum sodium concentration. The factor 1 is added to the patient's total body water in the equation to account for the volume of the infused solution. Although conferring mathematical precision, the computational consequences of this factor are meaningful for relatively small values of total body water (i.e., in children and infants). Total body water can be approximated by 60% and 50% of body weight in non-elderly men and women, respectively. Of course, the reliability of the equation's projection is augmented if refined estimates of total body water are utilized that consider a number of parameters, including gender, age, fat content, and state of hydration. The sodium concentration of the most frequently used infusates is presented in Table 2.

We should stress that, like all conventional formulas (Table 1), the new equation assumes that the only variable disturbing the body's content of water and cations during the course of the infusion is the administered infusate itself. Of course, this assumption is virtually never accurate, because even an anuric patient incurs fecal and insensible losses of water and electrolytes. Appropriate adjustments in the fluid prescription must, therefore, be made as guided by clinical observations and laboratory monitoring.

Let us now illustrate the application of the equation in the management of dysnatremic patients by examining the utility and limitations of this novel approach. The treatment prescriptions that follow are intended to exemplify the equation's application and should not be taken as rigid guidelines for management of abnormalities of serum sodium concentration.

Table 3 Application of new equation in managing hypernatremia

	$\Delta[Na^+]_s = \frac{Na_{inf} - Na_s}{TBW \quad 1}$
	78-year-old man with $[Na^+]_s$ 165 mEq/l, body weight 72 kg; TBW, $0.5 \times 72 = 36$ l
Setting # 1.	Euvolemic hypernatremia Selected solution is 5 % dextrose in water (sodium concentration 0 mEq/l)
	$\Delta[Na^+]_s = \frac{0 - 165}{36 \quad 1} = -4.5$ mEq/l per 1 l of infusate
	For a goal of $\Delta[Na^+]_s$ –12 mEq/l/24 h, $-12 \div -4.5 = 2.7$ l of infusate are required
Setting # 2.	Hypovolemic hypernatremia Selected solution is quarter-normal saline (sodium concentration 34 mEq/l)
	$\Delta[Na^+]_s = \frac{34 - 165}{36 \quad 1} = -3.5$ mEq/l per 1 l of infusate
	For a goal of $\Delta[Na^+]_s$ –12 mEq/l/24 h, $-12 \div -3.5 = 3.4$ l of infusate are required
Setting # 3.	Hypovolemic hypernatremia Selected solution is half-normal saline (sodium concentration 77 mEq/l)
	$\Delta[Na^+]_s = \frac{77 - 165}{36 \quad 1} = -2.4$ mEq/l per 1 l of infusate
	For a goal of $\Delta[Na^+]_s$ –12 mEq/l/24 h, $-12 \div -2.4 = 5.0$ l of infusate are required
Setting # 4.	Euvolemic hypernatremia Selected solution is normal saline (sodium concentration 154 mEq/l)
	$\Delta[Na^+]_s = \frac{154 - 165}{36 \quad 1} = -0.3$ mEq/l per 1 l of infusate

Because of the patient's age and prevailing dehydration, estimated TBW is taken as 50 % of body weight, rather than the usual 60 %. In each setting, ongoing renal and extrarenal fluid losses should be added to the overall fluid prescription

Utility

Projecting the infusate's impact on $[Na^+]_s$

The proposed formula allows an expedient projection of the effects of the selected infusate on the patient's serum sodium concentration, the parameter of concern. As such, it provides instant feedback about the soundness of the therapeutic decision made. The calculation – a simple arithmetic computation – is performed for a unit dose, i. e., 1 l of the infusate; the cumulative amount to be administered over a particular time interval can then be easily computed by dividing the desired $\Delta[Na^+]_s$ at the end of this period by the projected $\Delta[Na^+]_s$ in response to administering 1 l of the infusate.

Consider Case 1, a 78-year-old man, who presents with fever, cough, tachypnea, and obtundation and is found to have a lobar pneumonia. His serum sodium concentration is 165 mEq/l and weight 72 kg. The treating physician diagnoses euvolemic hypernatremia and, therefore, the decision is made to correct the disorder by infusing 5 % dextrose in water [5–7]. Because of the patient's age and prevailing dehydration, the estimated total body water of the patient at the time of the evaluation is probably closer to 50 % of his body weight (rather than the usual 60 % estimate for normal young men [5], i. e., 0.5×72 kg, or 36 l. According to the conventional approach, implementation of the therapeutic decision made requires that the practitioner apply the patient's data to formula # 1 of Table 1, which estimates the prevailing water deficit. This calculation will yield a water deficit of 6.4 l that must be repaired to return the patient's serum sodium concentration to the level of 140 mEq/l, barring further changes in the body's water and sodium content. The treating physician might then elect to repair this water deficit over the next 48 h with an infusion of 5 % dextrose in water at a calculated constant rate [3]. Note, however, that this approach, although theoretically accurate, does not provide the physician with a convenient and direct insight of the interim changes in serum sodium concentration that are anticipated as a result of the ongoing fluid treatment. Furthermore, any plan of fluid therapy projected over a time period of 48 h or longer is bound to have limited practical reliability because of intercurrent fluid losses and the vagaries of the underlying disease.

Let us now approach Case 1 according to the proposed novel method. The treating physician has elected to manage the hypernatremic patient with 5 % dextrose in water and wishes to project the change in the serum sodium concentration following the administration of 1 l of this solution. Application of the proposed equation to this clinical setting (Table 3, setting # 1) will yield a projected decrease in the patient's serum sodium concentration of 4.5 mEq/l. Now, if the physician's treatment goal is a decrease in serum sodium concentration of 12 mEq/l over the first 24-h period (i. e., a correction rate of 0.5 mEq/l per h), then 2.7 l of this infusate should be administered (Table 3, # 1). Obviously, ongoing renal and extrarenal fluid losses should be replaced and therefore added to the overall fluid prescription. Note that this simple and convenient approach maintains a sharp focus on the expected interval changes in the serum sodium concentration, i. e., the perturbation under treatment, as a result of the specific therapeutic maneuver employed. We should emphasize, however, that the infusion rate selected on the basis of the proposed computation is a reasonable but imprecise projection. Therefore, frequent monitoring of the patient's laboratory values, initially at 3- to 4-h intervals, is mandatory. Reapplication of the proposed formula in the light of the observed change in the patient's serum sodium concentration and overall clinical status can guide further management.

Table 4 Application of new equation in managing hyponatremia

$$\Delta[Na^+]_s = \frac{Na_{inf} \quad Na_s}{TBW \quad 1}$$

Setting # 1. Symptomatic 52-year-old woman with SIADH; $[Na^+]_s$ 108 mEq/l, body weight 65.5 kg; TBW, $0.5 \times 65.5 = 32.8$ l
Selected therapy is water restriction and hypertonic saline (sodium concentration 513 mEq/l)

$$\Delta[Na^+]_s = \frac{513 \quad 108}{32\,8 \quad 1} = 12 \text{ mEq/l per 1 l of infusate}$$

For *initial rate* of correction of 1 mEq/l/h, $1{,}000 \div 12 = 83$ ml/h are required

Setting # 2. Asymptomatic 65-year-old man with SIADH; $[Na^+]_s$ 115 mEq/l, body weight 76 kg; TBW, $0.6 \times 76 = 45.6$ l
Selected therapy is water restriction and normal saline (sodium concentration 154 mEq/l)

$$\Delta[Na^+]_s = \frac{154 \quad 115}{45\,6 \quad 1} = 0.8 \text{ mEq/l per 1 l of infusate}$$

Setting # 3. Asymptomatic hypovolemic hyponatremia
35-year-old man with $[Na^+]_s$ 113 mEq/l, body weight 70 kg; TBW, $0.6 \times 70 = 42$ l
Selected solution is normal saline (sodium concentration 154 mEq/l)

$$\Delta[Na^+]_s = \frac{154 \quad 113}{42 \quad 1} = 1 \text{ mEq/l per 1 l of infusate}$$

On the other hand, the physician might surmise that in addition to pure dehydration, Case 1 features a small element of extracellular fluid (ECF) volume contraction (that is, sodium deficit). Therefore, the decision might be made to infuse quarter-normal saline (commercially available as 0.2 % sodium chloride in 5 % dextrose in water) rather than 5 % dextrose in water. What will be the quantitative impact on the patient's hypernatremia of administering this solution? As it happens, there is currently no convenient tool to assist the physician in this estimation. Consequently, physicians usually resort to an empiric, non-quantitative approach to this very common situation of fluid management. Our experience indicates that practitioners actually have widely disparate and often unrealistic expectations of the hypernatremia-corrective potential of this and other sodium-containing solutions. The proposed method offers a simple and expedient remedy to this situation. Utilizing the proposed equation, we can easily project that 1 l of the quarter-normal saline solution will decrease the serum sodium concentration of our patient by 3.5 mEq/l (Table 3, setting # 2). Accordingly, if the physician is still aiming at lowering the serum sodium concentration by 12 mEq/l over the first 24-h period, then 3.4 l of quarter-normal saline should be infused (Table 3, setting # 2). Again, appropriate adjustments in the fluid prescription should be made to compensate for ongoing fluid losses.

What if the physician had felt that the prevailing ECF volume contraction in Case 1 is more severe and, therefore, had chosen to administer half-normal saline as initial treatment? How much of a decrease in the patient's serum sodium concentration would be effected by 1 l of this infusate? Contrary to the conventional approach, the proposed equation allows an easy answer to this question. As depicted in Table 3, setting # 3, infusion of 1 l of half-normal saline is predicted to decrease the serum sodium concentration of our patient by 2.4 mEq/l. Thus, 5 l of this solution will be required to achieve the projected 12 mEq/l overall decrease in serum sodium concentration over the first 24-h period (Table 3, setting # 3). Alternatively, the equation allows the physician to incorporate solutions of variable sodium concentration to the fluid prescription in the context of offering reasonable projections of their anticipated impact on the serum sodium concentration. Indeed, the computations depicted in Table 3, settings # 1–3, demonstrate explicitly the remarkable utility of the proposed equation to quantitate with ease the differential impact of various solutions on the correction of hypernatremia, a heretofore unavailable guide to clinical management. This information is indeed most important, as the rate of correction of hypernatremia must be controlled lest serious complications or death might ensue [5, 7].

Similarly, the proposed equation can conveniently aid fluid prescription for correcting hyponatremia. Consider Case 2, a 52-year-old woman with lung carcinoma and the syndrome of inappropriate antidiuretic hormone secretion (SIADH), who presents with severe confusion and lethargy. Her serum sodium concentration is 108 mEq/l and weight 65.5 kg. The physician caring for the patient has selected water restriction and hypertonic saline (3 % sodium chloride containing 513 mEq/l of sodium, Table 2) for initial management. The estimated total body water of the patient is 0.5×65.5 kg or 32.8 l. The conventional approach for estimating the amount of exogenous sodium required to raise a patient's serum sodium concentration to a desired higher level employs formula # 3 of Table 1. After this calculation is made the treating physician must then convert the mEq of sodium required into the corresponding volume of the 3 % sodium chloride solution. Finally, consideration of the desired rate of correction of the prevailing hyponatremia will yield the estimated rate of infusion of this solution.

Contrast now the complex and circuitous nature of the conventional approach with the simplicity and directness of the proposed method. As noted, the treating physician has selected water restriction and 3 % sodium chloride for initial management of this patient with symptomatic hyponatremia. Application of the proposed equation to this clinical setting (Table 4, setting # 1) will yield a projected increase in the patient's serum sodium concentration of 12 mEq/l following the ad-

ministration of 1 l of this solution. Because of the symptomatic but presumably chronic nature of the patient's hyponatremia, one must strike a balance between the need for relief of cerebral edema and the risk of neurologic sequelae (specifically central pontine myelinolysis) from overly zealous correction of the hyponatremia [4, 8]. Thus, if the physician has decided on an initial rate of correction on the order of 1 mEq/l per h [3], then an *initial rate* of 3% sodium chloride administration of 83 ml/h can easily be computed (Table 4, setting # 1). Of course, the *subsequent rate* of the infusion must be guided by close monitoring of the patient's condition and laboratory values (initially at hourly intervals), the prevailing urinary volume and cationic (that is sodium and potassium) content, and the necessity to limit both the ECF volume expansion (e.g., use of a loop diuretic) and the absolute increase in the patient's serum sodium concentration to about 12 mEq/l over the first 24-h period [3]. One cannot overemphasize the importance of frequent monitoring of the patient's serum sodium concentration, especially during the initial stages of treatment, in making subsequent adjustments in the fluid prescription. Further application of the equation utilizing the newly determined serum sodium concentration will aid the physician in adjusting, conveniently and expeditiously, the rate of the infusion.

Reexamining the appropriateness of the selected fluid prescription

The proposed equation subjects to scrutiny the appropriateness of the selected treatment plan. Thus, in many instances, we have witnessed pseudoresistance or even aggravation of the elevated serum sodium level of patients with euvolemic hypernatremia following the inadvertent administration of normal saline. Such an infusion is ordered on the physician's belief that this solution will provide a desirable, slow-paced correction of the prevailing hypernatremia. This approach entails, of course, a therapeutic pitfall. First, this type of hypernatremia requires simply replenishment of the existing water deficit. Second, application of the proposed equation to the data of Case 1 promptly demonstrates the minimal change in the serum sodium concentration, that is a decrease of only 0.3 mEq/l, following infusion of 1 l of 0.9% sodium chloride (Table 3, setting # 4)! Thus, utilization of the proposed approach can expose clearly the ineffectiveness of administering normal saline as a treatment of euvolemic hypernatremia. Such a warning might well have critical clinical implications, as ongoing hypotonic fluid losses might outpace this fluid prescription, thereby promoting aggravation of the hypernatremia. By contrast, the conventional approach offers no expedient way to ascertain the fallacy of this therapeutic maneuver.

By way of analogy, on many occasions we have observed that patients with SIADH and asymptomatic hyponatremia of variable severity are prescribed normal saline (i.e., 0.9% sodium chloride) in the mistaken belief that the sodium-rich infusate relative to the patient (e.g., 154 vs 115 mEq/l) will achieve substantial correction of the patient's hyponatremia. As a rule, this treatment meets with failure as a meager rise in the patient's serum sodium concentration during the course of the infusion is followed by a fall to a level below the original baseline! Indeed, application of the proposed approach embodied in the equation to such a case (e.g., 65-year-old man weighing 76 kg, baseline $[Na^+]_s$ 115 mEq/l, and estimated total body water of 0.6×76 kg or 45.6 l) demonstrates vividly the futility of treating the hyponatremia of SIADH with normal saline (Table 4, setting # 2). As can be seen in the Table, retention of 1 l of 0.9% sodium chloride (and assuming no other fluid and electrolyte gains or losses) is projected to increase this patient's serum sodium concentration by only 0.8 mEq/l. The availability of this information might lead the practitioner to reexamine the appropriateness of the selected option. Moreover, the eventual worsening of the hyponatremia to levels below the original baseline following the inappropriate administration of normal saline reflects the fact that in these patients the administered sodium chloride load will be promptly excreted in the urine at an osmolality that exceeds that of the infusate; consequently, net retention of water will ensue [9]. In fact, the mainstay of the treatment of the asymptomatic patient with SIADH is water restriction.

Limitations

As noted at the outset, an important limitation of the proposed equation is that it considers the patient as a closed system that incurs no gain or loss of water and electrolytes, other than the administered infusate during the time frame of the infusion. This very limitation is, of course, shared by the conventional formulas that estimate the cumulative amounts of sodium and water required for the correction of dysnatremias (Table 1) [1–5]. In this regard, the proposed equation and the conventional formulas provide quantitative tools for guiding the repair of existing abnormalities in serum sodium concentration. They cannot anticipate future changes in the body's fluid and electrolyte economy. Since ongoing renal and extrarenal fluid losses are commonly substantial in dysnatremic patients, the physician must make appropriate allowances in the management plan. Such a provision should permit the physician to compensate for this limitation. On the contrary, failure to do so will impose a substantial deviation of the actual level of serum sodium concentration obtained at the end of the infusion from the value projected by the equation.

Like the conventional formulas, the proposed equation includes a term for the patient's total body water. Consequently, the reliability of the computation depends on the accuracy of this term. Yet, the clinical estimate of total body water is a rough approximation at best. As noted earlier, every effort should be made to arrive at the best possible estimate of the patient's total body water by considering all the relevant parameters. Because of this limitation and the virtually ever-present ongoing fluid losses referred to above, effective management of the dysnatremias mandates frequent monitoring of the patient's clinical condition and laboratory data.

Further, we should reemphasize that the proposed equation, indeed all relevant formulas (Table 1), do not obviate the need for a sound understanding of the pathophysiology of salt and water balance as prerequisite to effective management of the dysnatremias. No equation can be used to select therapy for the dysnatremic patient. Far from serving as substitutes for rigorous pathophysiologic analysis, these formulas should only be used as auxiliary instruments designed to facilitate the implementation of the selected fluid therapy. Indeed, there are no shortcuts to rigorous pathophysiologic reasoning and sound clinical judgement for optimal management of the dysnatremias. To underscore this critical point, let us consider a 35-year-old man, who is being treated for asymptomatic hypovolemic hyponatremia caused by gastrointestinal fluid losses and continued free water ingestion. His serum sodium concentration is 113 mEq/l and body weight is 70 kg (estimated total body water, $0.6 \times 70 = 42$ l). The treating physician has appropriately selected the infusion of normal saline for this patient's management. Application of the proposed equation to the patient's data allows the physician to conveniently estimate that 1 l of the selected infusate will raise the serum sodium concentration by 1 mEq/l (Table 4, setting # 3). This information can be used conveniently in conjunction with hemodynamic indices in guiding the patient's fluid therapy. Indeed, the initially meager pace of correction of the prevailing hyponatremia forecasted by the equation should alert the practitioner to the continued vulnerability of the patient for advancing to more severe degrees of hyponatremia should he continue free water ingestion. On the other hand, it would be fallacious for the physician to surmise that the rate of correction of the hyponatremia in response to continued saline administration will remain at the slow pace indicated above. Indeed, as soon as the patient's volume status nears restitution, the non-osmotic stimulation of antidiuretic hormone release will cease, thereby allowing production of dilute urine and promoting correction of the hyponatremia at a substantially brisker pace.

Certainly, one might take the iconoclastic position of banning the use of all formulas, conventional and novel alike, in managing the dysnatremias in favor of applying solely pathophysiologic reasoning, clinical judgement and frequent monitoring of the patient's condition and laboratory data. We do not subscribe to this extreme view. Rather, as emphasized above, we consider the conventional formulas depicted in Table 1 and, particularly, the derived novel equation as useful, ancillary instruments that provide quantitative guidance in implementing the selected treatment plan.

In conclusion, we have introduced an equation derived from a computation of the changes in body composition incurred as a result of an infusion and have examined its utility in the management of the dysnatremias. On the basis of a simple arithmetic calculation, the equation allows projection of the impact of a unit dose, i.e., 1 l of the selected infusate on the disturbed serum sodium concentration. In accordance with the equation, the expected change in the patient's serum sodium concentration in response to 1 l of any infusate ($\Delta[Na^+]_s$) is obtained by subtracting the sodium concentration of the patient's serum from the sodium concentration of the infusate, each expressed in mEq/l, and dividing the result by the patient's estimated total body water expressed in liters (adding 1 l to account for the volume of the infusate). The cumulative amount of the particular infusate to be administered over the course of any given time period can then be easily computed by dividing the desired $\Delta[Na^+]_s$ at the end of the period by the calculated $\Delta[Na^+]_s$ effected by 1 l of the infusate, as derived by the equation. In so doing, the equation maintains a sharp focus on the parameter of concern, the serum sodium concentration.

The equation is not a means for formulating therapy but rather an ancillary instrument that can assist the physician in implementing the selected treatment plan. Advantages of the novel equation over the conventional formulas include the following:

1. It is applicable to both hypernatremia and hyponatremia.
2. It links directly the amount of the administered infusate with the anticipated change in the patient's serum sodium concentration (expressed in mEq/l).
3. It projects the impact of solutions of variable sodium concentration on the patient's serum sodium concentration.
4. It focuses attention on a shorter time frame of the patient's management.
5. On occasion, it can reveal unrealistic expectations about the corrective potential of a particular infusate on certain dysnatremias, and thus compel the physician to reexamine the appropriateness of the selected fluid prescription.

Assuming that its limitations are properly understood, the proposed equation can provide a significant measure of assistance in the management of the dysnatremias.

Acknowledgements The authors are indebted to Debby S. Verrett for skillful assistance in preparing the manuscript.

Appendix

Sodium salts represent the principal extracellular osmoles. Since the two major body fluid compartments, extracellular and intracellular, are in osmotic equilibrium, total body osmoles may be conveniently estimated as the product of total body water and the serum concentration of sodium salts (i.e., $TBW \times (2 \times [Na^+]_s)$). Similarly, osmoles available in 1 l of a sodium-containing infusate represent the product of the volume and concentration of sodium salts in the solution (i.e., $1\,l \times (2 \times [Na^+]_{inf})$). As our interest centers on the estimation of projected changes in serum $[Na^+]$ in response to administering a unit dose, i.e., 1 l of different infusates, we shall disregard the osmolar contribution of the anions and only compute the osmoles accounted for by the cation (i.e., sodium). Thus, total body cationic osmoles (TBCO), infusate cationic osmoles per liter of fluid (ICO), and total body cationic osmoles after retention of 1 l of the infusate (TBICO) are calculated as follows:

$$TBCO = TBW \times {}_{initial}[Na^+]_s \quad \text{(Eq. A-1)}$$
$$ICO = 1l \times [Na^+]_{inf} \quad \text{(Eq. A-2)}$$
$$TBICO = TBCO + ICO \quad \text{(Eq. A-3)}$$

where TBW and ${}_{initial}[Na^+]_s$ are the baseline levels of total body water and serum sodium concentration of the patient, expressed in liters and mEq/l, respectively. The serum sodium concentration of the patient after retention of 1 l of infusate, designated as ${}_{final}[Na^+]_s$ is obtained as follows:

$${}_{final}[Na^+]_s = \frac{TBCO \quad ICO}{TBW \quad 1l} \quad \text{(Eq. A-4)}$$

Substituting the terms TBCO and ICO according to Eqs. A-1 and A-2, respectively, we obtain:

$${}_{final}[Na^+]_s = \frac{TBW \quad {}_{initial}Na_s \quad 1l \quad Na_{inf}}{TBW \quad 1l} \quad \text{(Eq. A-5)}$$

The change in serum sodium concentration of the patient ($\Delta[Na^+]_s$) as a result of the infusion is defined as,

$$\Delta[Na^+]_s = {}_{final}[Na^+]_s - {}_{initial}[Na^+]_s \quad \text{(Eq. A-6)}$$

Substituting the term ${}_{final}[Na^+]_s$ according to Eq. A-5, we obtain:

$$\Delta[Na^+]_s = \frac{TBW \quad {}_{initial}Na_s \quad 1l \quad Na_{inf}}{TBW \quad 1l} - {}_{initial}[Na^+]_s \quad \text{(Eq. A-7)}$$

Further, we insert a common denominator for the equation:

$$\Delta[Na^+]_s = \frac{TBW \quad {}_{initial}Na_s \quad 1l \quad Na_{inf} \quad {}_{initial}Na_s \quad TBW \quad 1l}{TBW \quad 1l} \quad \text{(Eq. A-8)}$$

Rearranging the numerator of the equation, we obtain:

$$\Delta[Na^+]_s = \frac{TBW \quad {}_{initial}Na_s \quad 1l \quad Na_{inf} \quad {}_{initial}Na_s \quad TBW \quad {}_{initial}Na_s \quad 1l}{TBW \quad 1l} \quad \text{(Eq. A-9)}$$

Finally, deleting from the numerator the term ${}_{initial}[Na^+]_s \times TBW$, as it is present twice with positive and negative signs, and rearranging, we obtain:

$$\Delta[Na^+]_s = \frac{Na_{inf} \quad {}_{initial}Na_s \quad 1l}{TBW \quad 1l} \quad \text{(Eq. A-10)}$$

Simplifying Eq. A-10, we obtain:

$$\Delta[Na^+]_s = \frac{Na_{inf} \quad Na_s}{TBW \quad 1l} \quad \text{(Eq. A-11)}$$

where $[Na^+]_s$ represents the initial $[Na^+]$ in the patient's serum, expressed in mEq/l. Although not evident in the simplified Eq. A-11, $\Delta[Na^+]_s$ is expressed in mEq/l, as indicated by Eq. A-10.

Demonstration of the validity and accuracy of Eq. A-11

1. Let us project the impact of retaining 1 l of quarter-normal saline (sodium concentration 34 mEq/l) on the $[Na^+]_s$ of a 78-year-old man presenting with a $[Na^+]_s$ of 165 mEq/l. Body weight is 72 kg.

a. Conventional approach

Initial TBW = 0.5 × body weight = 0.5 × 72 = 36 l
Final TBW = 36 + 1 = 37 l
Initial total body cationic osmoles = 165 × 36 = 5,940 mEq
Final total body cationic osmoles = 5,940+34 = 5,974 mEq
Final $[Na^+]_s$ = 5,974 ÷ 37 = 161.46 mEq/l
$\Delta[Na^+]_s$ = 161.46 – 165 = –3.54 mEq/l

b. New approach (based on Eq. A-11)

$$\Delta[Na^+]_s = \frac{Na_{inf} \quad Na_s}{TBW \quad 1} = \frac{34 \quad 165}{36 \quad 1} = -3.54 \text{ mEq/l}$$

2. Let us project the impact of retaining 1 l of 5 % dexrose in water (sodium concentration 0 mEq/l) on the $[Na^+]_s$ of a 78-year-old man presenting with a $[Na^+]_s$ of 165 mEq/l. Body weight is 72 kg.

a. Conventional approach

Initial TBW = 0.5 × body weight = 0.5 × 72 = 36 l
Final TBW = 36 + 1 = 37 l
Initial total body cationic osmoles = 165 × 36 = 5,940 mEq
Final total body cationic osmoles = 5,940 + 0 = 5,940 mEq
Final $[Na^+]_s$ = 5,940 ÷ 37 = 160.54 mEq/l
$\Delta[Na^+]_s$ = 160.54 – 165 = –4.46 mEq/l

b. New approach (based on Eq. A-11)

$$\Delta[Na^+]_s = \frac{Na_{inf} - Na_s}{TBW + 1} = \frac{0 - 165}{36 + 1} = -4.46 \text{ mEq/l}$$

3. Let us project the impact of retaining 1 l of hypertonic saline (sodium concentration 513 mEq/l) on the $[Na^+]_s$ of a symptomatic 52-year-old woman with SIADH presenting with a $[Na^+]_s$ of 108 mEq/l. Body weight is 65.5 kg.

a. Conventional approach

Initial TBW = 0.5 × body weight = 0.5 × 65.5 = 32.8 l
Final TBW = 32.8 + 1 = 33.8 l
Initial total body cationic osmoles = 108 × 32.8 l = 3,542.4 mEq
Final total body cationic osmoles = 3,542.4 + 513 = 4,055.4 mEq
Final $[Na^+]_s$ = 4,055.4 ÷ 33.8 = 119.98 mEq/l
$\Delta[Na^+]_s$ = 119.98 – 108 = 11.98 mEq/l

b. New approach (based on Eq. A-11)

$$\Delta[Na^+]_s = \frac{Na_{inf} - Na_s}{TBW + 1} = \frac{513 - 108}{32.8 + 1} = -11.98 \text{ mEq/l}$$

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Nephrol Dial Transplant (2002) 17: 1176–1180

Nephrology Dialysis Transplantation

Hypothesis

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

Noha R. Barsoum and Barton S. Levine

Department of Medicine, UCLA School of Medicine, Nephrology Section, VAGLAHS, West Los Angeles, CA, USA

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]:

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

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

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

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, Adrogue 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:

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

where ΔSerum [Na^+] is the change in serum Na^+ concentration, $[Na^+]_{inf}$ is the concentration of infusate Na^+, and $[Na^+]_s$ 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,

Correspondence and offprint requests to: Barton Levine, VAGLAHS, West Los Angeles, Nephrology Section 111L, 11301 Wilshire Boulevard, Los Angeles, CA 90073, USA.
Email: barton.lavine@med.va.gov

Published on behalf of European Renal Association–European Dialysis and Transplant Association

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:

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

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 periphral oedema. Neurological examination revealed him to be remarkable for lethargy and drowsiness, but was otherwise non-focal. Review of fluid input and ouput 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
$[Na^+]_{inf}$ (mEq/l)	154	154
$[K^+]_{inf}$ (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
ΔSerum $[Na^+]$ (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; $[Na^+]_{Inf}$, infusate Na^+ concentration; $[K^+]_{Inf}$, 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 Adrogue 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 Adrogue and Madias, our formula is:

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

where V_i is the volume of infusate in litres, V_u is the urine output in litres, ΔV is $V_i - V_u$, $[Na^+]_{inf}$ is the Na^+ concentration in the infusate, $[Na^+]_u$ is the urinary Na^+ concentration, $[Na^+]_s$ 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:

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

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:

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

Discussion

In such a simplified form, Equation 8 can be used to quickly estimate the change in $[Na^+]_s$ 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 $[Na^+]$. 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 $[Na^+]$ 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 $[Na^+]$; the patient's serum $[Na^+]$ 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 $[Na^+]$ 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:

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

where $[Na^+ + K^+]_o$ 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 is serum $[Na^+]$ 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 $[Na^+]$ 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 $[Na^+]_s$ 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.

Acknowledgements. We wish to acknowledge the editorial assistance and suggestions of Arnold Felsenfeld.

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Received for publication: 15.11.01
Accepted in revised form: 8.3.02

Appendix

The input formula

Adrogue 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:

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

Similarly:

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

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

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

Similarly:

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

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 $[Na^+]$ ($[Na^+]_F$), TBICO is divided by TBW + 1 l from infusate:

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

or

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

Substituting the terms:

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

Since the change in serum $[Na^+]$ (ΔSerum $[Na^+]$) is the difference between $[Na^+]_F$ and the initial $[Na^+]_s$:

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

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

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

Using a common denominator:

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

Simplifying the formula:

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

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

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

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

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

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

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

The output formula:

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

Similarly:

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

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 $[Na^+]_F$:

$$[Na^+]_F = TBUCO/(TBW - 1\ l)$$

or

$$[Na^+]_F = (TBCO - UCO)/(TBW - 1\ l)$$

Substituting the terms:

$$[Na^+]_F = [([Na^+]_s \times TBW) - ([Na^+]_u \times 1\ l)]/(TBW - 1\ l)$$

The change in serum $[Na^+]$ is the difference between $[Na^+]_F$ and $[Na^+]_s$:

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

Substituting the appropriate terms for $[Na^+]_F$:

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

Rearranging the formula and using a common denominator:

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

Rearranging the numerator:

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

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

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

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

$$\Delta\text{Serum } [Na^+] = ([Na^+]_s - [Na^+]_u)/(TBW - 1)$$

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

The final formula becomes:

$$\Delta\text{Serum } [Na^+] = [V_u([Na^+]_s - [Na^+]_u)]/(TBW - 1)$$

Factoring in the contribution of K^+:

$$\Delta\text{Serum } [Na^+] = [V_u([Na^+]_s - [Na^+ + K^+]_u)]/(TBW - 1) \quad (B)$$

Based on the above calculations, one would expect the net change in serum $[Na^+]$ 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 $[Na^+]$ 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 TBW + 1 and 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.

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

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

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

If the patient is aneuric then the formula reduces to:

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

which is the original formula introduced by Adrogue and Madias.

Review Article

Primary Care

HYPONATREMIA

HORACIO J. ADROGUÉ, M.D.,
AND NICOLAOS E. MADIAS, M.D.

HYPONATREMIA is defined as a decrease in the serum sodium concentration to a level below 136 mmol per liter. Whereas hypernatremia always denotes hypertonicity, hyponatremia can be associated with low, normal, or high tonicity.[1,2] Effective osmolality or tonicity refers to the contribution to osmolality of solutes, such as sodium and glucose, that cannot move freely across cell membranes, thereby inducing transcellular shifts in water.[3] Dilutional hyponatremia, by far the most common form of the disorder, is caused by water retention. If water intake exceeds the capacity of the kidneys to excrete water, dilution of body solutes results, causing hypo-osmolality and hypotonicity (Fig. 1B, 1E, 1F, and 1G). Hypotonicity, in turn, can lead to cerebral edema, a potentially life-threatening complication.[4] Hypotonic hyponatremia can be associated, however, with normal or even high serum osmolality if sufficient amounts of solutes that can permeate cell membranes (e.g., urea and ethanol) have been retained (Fig. 1C). Importantly, patients who have hypotonic hyponatremia but normal or high serum osmolality are as subject to the risks of hypotonicity as are patients with hypo-osmolar hyponatremia.

The nonhypotonic hyponatremias are hypertonic (or translocational) hyponatremia, isotonic hyponatremia, and pseudohyponatremia.[1,2] Translocational hyponatremia results from a shift of water from cells to the extracellular fluid that is driven by solutes confined in the extracellular compartment (as occurs with hyperglycemia or retention of hypertonic mannitol); serum osmolality is increased, as is tonicity, the latter causing dehydration of cells (Fig. 1D). Retention in the extracellular space of large volumes of isotonic fluids that do not contain sodium (e.g., mannitol) generates iso-osmolar and isotonic hyponatremia but no transcellular shifts of water. Pseudohyponatremia is a spurious form of iso-osmolar and isotonic hyponatremia identified when severe hypertriglyceridemia or paraproteinemia increases substantially the solid phase of plasma and the sodium concentration is measured by means of flame photometry.[1,2] The increasing availability of direct measurement of serum sodium with the ion-specific electrode has all but eliminated this laboratory artifact.[5]

A common clinical problem, hyponatremia frequently develops in hospitalized patients.[6] Although morbidity varies widely in severity, serious complications can arise from the disorder itself as well as from errors in management. In this article, we focus on the treatment of hyponatremia, emphasizing a quantitative approach to its correction.

CAUSES

Hypotonic (dilutional) hyponatremia represents an excess of water in relation to existing sodium stores, which can be decreased, essentially normal, or increased (Fig. 1). Retention of water most commonly reflects the presence of conditions that impair renal excretion of water[1,7,8]; in a minority of cases, it is caused by excessive water intake, with a normal or nearly normal excretory capacity (Table 1).[7]

Conditions of impaired renal excretion of water are categorized according to the characteristics of the extracellular-fluid volume, as determined by clinical assessment (Table 1).[9] With the exception of renal failure, these conditions are characterized by high plasma concentrations of arginine vasopressin despite the presence of hypotonicity.[10,11] Depletion of potassium accompanies many of these disorders and contributes to hyponatremia, since the sodium concentration is determined by the ratio of the "exchangeable" (i.e., osmotically active) portions of the body's sodium and potassium content to total body water (Fig. 1G).[12-14] Patients with hyponatremia induced by thiazides can present with variable hypovolemia or apparent euvolemia, depending on the magnitude of the sodium loss and water retention.[1,15-17]

Excessive water intake can cause hyponatremia by overwhelming normal water excretory capacity (e.g., primary polydipsia) (Table 1). Frequently, however, psychiatric patients with excessive water intake have plasma arginine vasopressin concentrations that are not fully suppressed and urine that is not maximally dilute, thus contributing to water retention.[18,19]

From the Department of Medicine, Baylor College of Medicine and Methodist Hospital, and the Renal Section, Department of Veterans Affairs Medical Center, Houston (H.J.A.); and the Department of Medicine, Tufts University School of Medicine, and the Division of Nephrology and Tupper Research Institute, New England Medical Center, Boston (N.E.M.). Address reprint requests to Dr. Madias at the Division of Nephrology, New England Medical Center, Box 172, 750 Washington St., Boston, MA 02111, or at nmadias@infonet.tufts.edu.

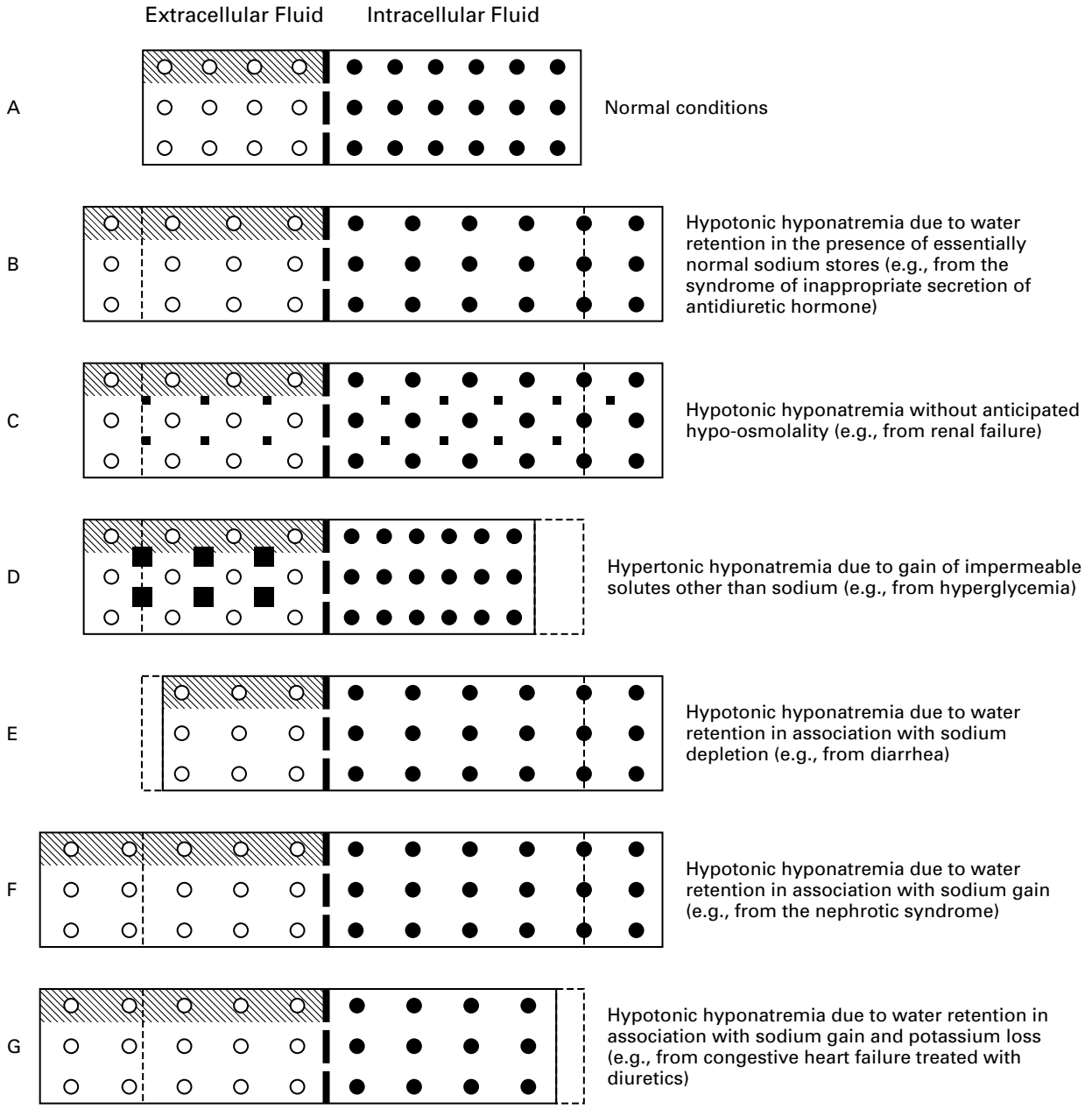

Figure 1. Extracellular-Fluid and Intracellular-Fluid Compartments under Normal Conditions and during States of Hyponatremia.

Normally, the extracellular-fluid and intracellular-fluid compartments make up 40 percent and 60 percent of total body water, respectively (Panel A). With the syndrome of inappropriate secretion of antidiuretic hormone, the volumes of extracellular fluid and intracellular fluid expand (although a small element of sodium and potassium loss, not shown, occurs during inception of the syndrome) (Panel B). Water retention can lead to hypotonic hyponatremia without the anticipated hypo-osmolality in patients who have accumulated ineffective osmoles, such as urea (Panel C). A shift of water from the intracellular-fluid compartment to the extracellular-fluid compartment, driven by solutes confined in the extracellular fluid, results in hypertonic (translocational) hyponatremia (Panel D). Sodium depletion (and secondary water retention) usually contracts the volume of extracellular fluid but expands the intracellular-fluid compartment. At times, water retention can be sufficient to restore the volume of extracellular fluid to normal or even above-normal levels (Panel E). Hypotonic hyponatremia in sodium-retentive states involves expansion of both compartments, but predominantly the extracellular-fluid compartment (Panel F). Gain of sodium and loss of potassium in association with a defect of water excretion, as they occur in congestive heart failure treated with diuretics, lead to expansion of the extracellular-fluid compartment but contraction of the intracellular-fluid compartment (Panel G). In each panel, open circles denote sodium, solid circles potassium, large squares impermeable solutes other than sodium, and small squares permeable solutes; the broken line between the two compartments represents the cell membrane, and the shading indicates the intravascular volume.

TABLE 1. CAUSES OF HYPOTONIC HYPONATREMIA.

IMPAIRED CAPACITY OF RENAL WATER EXCRETION

Decreased volume of extracellular fluid

- Renal sodium loss
  - Diuretic agents
  - Osmotic diuresis (glucose, urea, mannitol)
  - Adrenal insufficiency
  - Salt-wasting nephropathy
  - Bicarbonaturia (renal tubular acidosis, disequilibrium stage of vomiting)
  - Ketonuria
- Extrarenal sodium loss
  - Diarrhea
  - Vomiting
  - Blood loss
  - Excessive sweating (e.g., in marathon runners)
  - Fluid sequestration in "third space"
    - Bowel obstruction
    - Peritonitis
    - Pancreatitis
    - Muscle trauma
    - Burns

Increased volume of extracellular fluid

- Congestive heart failure
- Cirrhosis
- Nephrotic syndrome
- Renal failure (acute or chronic)
- Pregnancy

Essentially normal volume of extracellular fluid

- Thiazide diuretics*
- Hypothyroidism
- Adrenal insufficiency
- Syndrome of inappropriate secretion of antidiuretic hormone
  - Cancer
    - Pulmonary tumors
    - Mediastinal tumors
    - Extrathoracic tumors
  - Central nervous system disorders
    - Acute psychosis
    - Mass lesions
    - Inflammatory and demyelinating diseases
    - Stroke
    - Hemorrhage
    - Trauma
  - Drugs
    - Desmopressin
    - Oxytocin
    - Prostaglandin-synthesis inhibitors
    - Nicotine
    - Phenothiazines
    - Tricyclics
    - Serotonin-reuptake inhibitors
    - Opiate derivatives
    - Chlorpropamide
    - Clofibrate
    - Carbamazepine
    - Cyclophosphamide
    - Vincristine
  - Pulmonary conditions
    - Infections
    - Acute respiratory failure
    - Positive-pressure ventilation
  - Miscellaneous
    - Postoperative state
    - Pain
    - Severe nausea
    - Infection with the human immunodeficiency virus
- Decreased intake of solutes
  - Beer potomania
  - Tea-and-toast diet

EXCESSIVE WATER INTAKE

- Primary polydipsia†
- Dilute infant formula
- Sodium-free irrigant solutions (used in hysteroscopy, laparoscopy, or transurethral resection of the prostate)‡
- Accidental intake of large amounts of water (e.g., during swimming lessons)
- Multiple tap-water enemas

*Sodium depletion, potassium depletion, stimulation of thirst, and impaired urinary dilution are implicated.

†Often a mild reduction in the capacity for water excretion is also present.

‡Hyponatremia is not always hypotonic.

Hyperglycemia is the most common cause of translocational hyponatremia (Fig. 1D). An increase of 100 mg per deciliter (5.6 mmol per liter) in the serum glucose concentration decreases serum sodium by approximately 1.7 mmol per liter, with the end result a rise in serum osmolality of approximately 2.0 mOsm per kilogram of water.[1] Retention of hypertonic mannitol, which occurs in patients with renal insufficiency, has the same effect. In both conditions, the resultant hypertonicity can be aggravated by osmotic diuresis; moderation of hyponatremia or frank hypernatremia can develop, since the total of the sodium and potassium concentrations in the urine falls short of that in serum.[20]

Massive absorption of irrigant solutions that do not contain sodium (e.g., those used during transurethral

prostatectomy) can cause severe and symptomatic hyponatremia. Reflecting the composition of the irrigant, the resultant hyponatremia can be either hypotonic (with an irrigant containing 1.5 percent glycine or 3.3 percent sorbitol) or isotonic (with an irrigant containing 5 percent mannitol). Whether the symptoms derive from the presence of retained solutes, the metabolic products of such solutes, hypotonicity, or the low serum sodium concentration itself remains unclear.[21,22]

The most common causes of severe hyponatremia in adults are therapy with thiazides, the postoperative state and other causes of the syndrome of inappropriate secretion of antidiuretic hormone, polydipsia in psychiatric patients, and transurethral prostatectomy.[1,17,23-25] Gastrointestinal fluid loss, ingestion of dilute formula, accidental ingestion of excessive water, and receipt of multiple tap-water enemas are the main causes of severe hyponatremia in infants and children.[17,26]

CLINICAL MANIFESTATIONS

Just as in hypernatremia, the manifestations of hypotonic hyponatremia are largely related to dysfunction of the central nervous system, and they are more conspicuous when the decrease in the serum sodium concentration is large or rapid (i.e., occurring within a period of hours).[27] Headache, nausea, vomiting, mus-

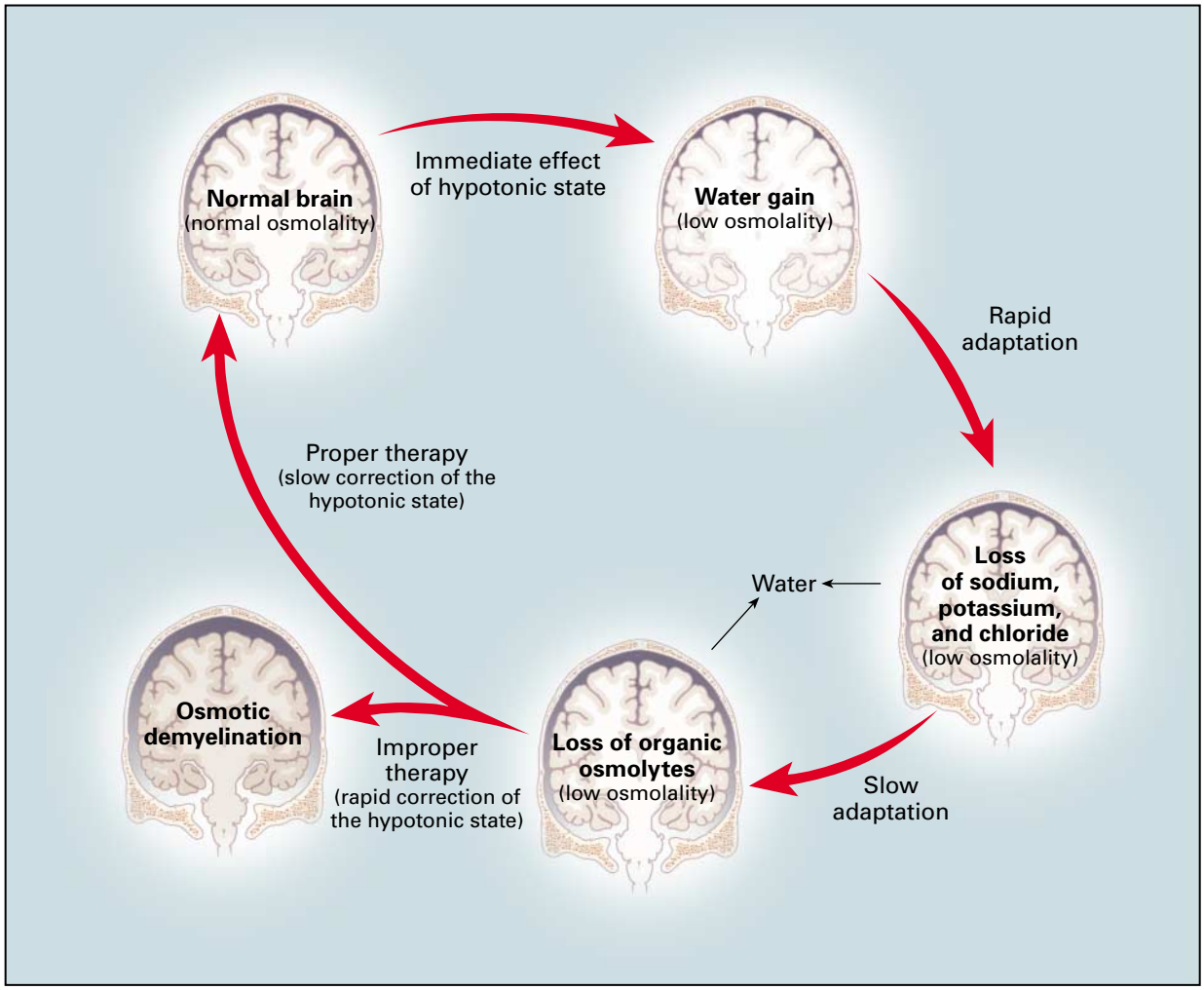

Figure 2. Effects of Hyponatremia on the Brain and Adaptive Responses.

Within minutes after the development of hypotonicity, water gain causes swelling of the brain and a decrease in osmolality of the brain. Partial restoration of brain volume occurs within a few hours as a result of cellular loss of electrolytes (rapid adaptation). The normalization of brain volume is completed within several days through loss of organic osmolytes from brain cells (slow adaptation). Low osmolality in the brain persists despite the normalization of brain volume. Proper correction of hypotonicity reestablishes normal osmolality without risking damage to the brain. Overly aggressive correction of hyponatremia can lead to irreversible brain damage.

cle cramps, lethargy, restlessness, disorientation, and depressed reflexes can be observed. Whereas most patients with a serum sodium concentration exceeding 125 mmol per liter are asymptomatic, those with lower values may have symptoms, especially if the disorder has developed rapidly.[4] Complications of severe and rapidly evolving hyponatremia include seizures, coma, permanent brain damage, respiratory arrest, brain-stem herniation, and death. These complications often occur with excessive water retention in patients who are essentially euvolemic (e.g., those recovering from surgery or those with primary polydipsia); menstruating women appear to be at particular risk.[23,28]

Hypotonic hyponatremia causes entry of water into the brain, resulting in cerebral edema (Fig. 2). Because the surrounding cranium limits expansion of the brain, intracranial hypertension develops, with a risk of brain injury. Fortunately, solutes leave brain tissues within hours, thereby inducing water loss and ameliorating brain swelling.[29,30] This process of adaptation by the brain accounts for the relatively asymptomatic nature of even severe hyponatremia if it develops slowly. Nevertheless, brain adaptation is also the source of the risk of osmotic demyelination.[31-33] Although rare, osmotic demyelination is serious and can develop one to several days after aggressive treatment of hyponatremia by any method, including water restriction alone.[34-36] Shrinkage of the brain triggers demyelination of pontine and extrapontine neurons that can cause neurologic dysfunction, including quadriplegia, pseudobulbar palsy, seizures, coma, and even death. Hepatic failure, potassium depletion, and malnutrition increase the risk of this complication.[1,37]

MANAGEMENT

The optimal treatment of hypotonic hyponatremia requires balancing the risks of hypotonicity against those of therapy.[28] The presence of symptoms and their severity largely determine the pace of correction.

Symptomatic Hypotonic Hyponatremia

Patients who have symptomatic hyponatremia with concentrated urine (osmolality, ≥200 mOsm per kilogram of water) and clinical euvolemia or hypervolemia require infusion of hypertonic saline (Table 2). This treatment can provide rapid but controlled correction of hyponatremia. Hypertonic saline is usually combined with furosemide to limit treatment-induced expansion of the extracellular-fluid volume. Because furosemide-induced diuresis is equivalent to a one-half isotonic saline solution, it aids in the correction of hyponatremia, as do ongoing dermal and respiratory fluid losses; anticipation of these losses should temper the pace of infusion of hypertonic saline. Obviously, electrolyte-free water intake must be withheld. In addition to hypertonic saline, hormone-

TABLE 2. FORMULAS FOR USE IN MANAGING HYPONATREMIA AND CHARACTERISTICS OF INFUSATES.

FORMULA*	CLINICAL USE
1. Change in serum $Na^+ = \frac{\text{infusate } Na^+ - \text{serum } Na^+}{\text{total body water} + 1}$	Estimate the effect of 1 liter of any infusate on serum Na^+
2. Change in serum $Na^+ = \frac{(\text{infusate } Na^+ + \text{infusate } K^+) - \text{serum } Na^+}{\text{total body water} + 1}$	Estimate the effect of 1 liter of any infusate containing Na^+ and K^+ on serum Na^+

INFUSATE	INFUSATE Na^+	EXTRACELLULAR-FLUID DISTRIBUTION
	mmol per liter	%
5% Sodium chloride in water	855	100†
3% Sodium chloride in water	513	100†
0.9% Sodium chloride in water	154	100
Ringer's lactate solution	130	97
0.45% Sodium chloride in water	77	73
0.2% Sodium chloride in 5% dextrose in water	34	55
5% Dextrose in water	0	40

*The numerator in formula 1 is a simplification of the expression (infusate Na^+ − serum Na^+) × 1 liter, with the value yielded by the equation in millimoles per liter.[38] The estimated total body water (in liters) is calculated as a fraction of body weight. The fraction is 0.6 in children; 0.6 and 0.5 in nonelderly men and women, respectively; and 0.5 and 0.45 in elderly men and women, respectively.[39] Normally, extracellular and intracellular fluids account for 40 and 60 percent of total body water, respectively.[39]

†In addition to its complete distribution in the extracellular compartment, this infusate induces osmotic removal of water from the intracellular compartment.

replacement therapy should be given to patients with suspected hypothyroidism or adrenal insufficiency after blood samples are obtained for diagnostic testing.[7,17] On the other hand, most patients with hypovolemia can be treated successfully with isotonic saline. Patients with seizures also require immediate anticonvulsant-drug therapy and adequate ventilation.[40]

Patients with symptomatic hyponatremia and dilute urine (osmolality, <200 mOsm per kilogram of water) but with less serious symptoms usually require only water restriction and close observation. Severe symptoms (e.g., seizures or coma) call for infusion of hypertonic saline.

There is no consensus about the optimal treatment of symptomatic hyponatremia.[28,40-49] Nevertheless, correction should be of a sufficient pace and magnitude to reverse the manifestations of hypotonicity but not be so rapid and large as to pose a risk of the development of osmotic demyelination. Physiologic considerations indicate that a relatively small increase in the serum sodium concentration, on the order of 5 percent, should substantially reduce cerebral edema.[9,50] Even seizures induced by hyponatremia can be stopped by rapid increases in the serum sodium concentration that average only 3 to 7 mmol per liter.[51,52] Most reported cases of osmotic demyelination occurred after rates of correction that exceeded 12 mmol per liter per day were used, but isolated cases occurred after corrections of only 9 to 10 mmol per liter in 24 hours or 19 mmol per liter in 48 hours.[34,35,40,48,53-56] After weighing the available evidence and the all-too-real risk of overshooting the mark, we recommend a targeted rate of correction that does not exceed 8 mmol per liter on any day of treatment. Remaining within this target, the initial rate of correction can still be 1 to 2 mmol per liter per hour for several hours in patients with severe symptoms. Should severe symptoms not respond to correction according to the specified target, we suggest that this limit be cautiously exceeded, since the imminent risks of hypotonicity override the potential risk of osmotic demyelination. Recommended indications for stopping the rapid correction of symptomatic hyponatremia (regardless of the method used) are the cessation of life-threatening manifestations, moderation of other symptoms, or the achievement of a serum sodium concentration of 125 to 130 mmol per liter (or even lower if the base-line serum sodium concentration is below 100 mmol per liter).[28,40] Long-term management of hyponatremia (described below) should then be initiated. Although faster rates of correction can be tolerated safely by most patients with acute symptomatic hyponatremia, there is no evidence that such an approach is beneficial.[40,57] Moreover, ascertaining the duration of hyponatremia is usually difficult.

How can the physician determine what the rate of infusion of the selected solution should be? This rate can be derived expediently by applying formula 1 in Table 2, the same formula used for managing hypernatremia, which projects the change in serum sodium elicited by the retention of 1 liter of any infusate.[38] Dividing the change in serum sodium targeted for a given treatment period by the output of this formula determines the volume of infusate required, and hence the rate of infusion. Table 2 also presents the sodium concentrations of commonly used infusates, their fractional distribution in the extracellular fluid, and clinical estimates of total body water.[39] We do not recommend use of the conventional formula for the correction of hyponatremia, as follows:

$$\text{sodium requirement} = \text{total body water} \times (\text{desired serum sodium concentration} - \text{current sodium concentration}).$$

The conventional formula requires a complicated procedure to convert the amount of sodium required to raise the sodium concentration to an infusion rate for the selected solution.

The cases described below illustrate the various forms of symptomatic hyponatremia and their management.

Hyponatremia in the Postoperative State

A previously healthy 32-year-old woman has three grand mal seizures two days after an appendectomy. She receives 20 mg of diazepam and 250 mg of phenytoin intravenously and undergoes laryngeal intubation with mechanical ventilation. Three liters of 5 percent dextrose in water had been infused during the first day after surgery, and the patient subsequently drank an unknown but substantial amount of water. Clinically, she is euvolemic, and she weighs 46 kg. She is stuporous and responds to pain but not to commands. The serum sodium concentration is 112 mmol per liter, the serum potassium concentration is 4.1 mmol per liter, serum osmolality is 228 mOsm per kilogram of water, and urine osmolality is 510 mOsm per kilogram of water. Hypotonic hyponatremia in this patient is a result of water retention caused by the impaired excretion of water that is associated with the postoperative state. Planned treatment includes the withholding of water, the infusion of 3 percent sodium chloride, and the intravenous administration of 20 mg of furosemide. The estimated volume of total body water is 23 liters (0.5×46).

According to formula 1 of Table 2, it is estimated that the retention of 1 liter of 3 percent sodium chloride will increase the serum sodium concentration by 16.7 mmol per liter ($[513-112] \div [23+1] = 16.7$). Given the seriousness of the patient's symptoms, the initial goal is to raise the serum sodium concentration by 3 mmol per liter over the next three hours; thus, 0.18 liter of hypertonic sodium chloride ($3 \div 16.7$), or 60 ml per hour, is required. Frequent monitoring of the serum sodium concentration, initially every two to three hours, is necessary in order

to make further adjustments in the amount of fluid administered. Although measuring urinary electrolytes can occasionally assist with management, it is generally unnecessary, and we do not recommend the routine use of this procedure.

Three hours later, the patient's serum sodium concentration is 115 mmol per liter. There have been no further seizures, but the level of responsiveness remains unchanged. The new goal is to increase the serum sodium concentration by an additional 3 mmol per liter over a period of six hours with the use of 3 percent sodium chloride; thus, the infusion rate is adjusted to 30 ml per hour. Nine hours after admission, the serum sodium concentration is 119 mmol per liter. There has been no seizure activity, and the patient now responds to simple commands. Hypertonic saline is discontinued, but close monitoring of the patient's clinical status and serum sodium concentration remains in effect. If the rate of correction is estimated to exceed the targeted rate, hypotonic solution should be administered.[58]

Hyponatremia in an Essentially Euvolemic State

A 58-year-old man with small-cell lung carcinoma presents with severe confusion and lethargy. Clinically, he is euvolemic, and he weighs 60 kg. The serum sodium concentration is 108 mmol per liter, the serum potassium concentration is 3.9 mmol per liter, serum osmolality is 220 mOsm per kilogram of water, the serum urea nitrogen concentration is 5 mg per deciliter (1.8 mmol per liter), the serum creatinine concentration is 0.5 mg per deciliter (44.2 μmol per liter), and urine osmolality is 600 mOsm per kilogram of water. The physician makes a provisional diagnosis of the tumor-induced syndrome of inappropriate secretion of antidiuretic hormone on the basis of the presence of hypotonic hyponatremia and concentrated urine in a euvolemic patient, the absence of a history of diuretic use, and the absence of clinical evidence of hypothyroidism or hypoadrenalism. The treatment plan includes water restriction, the infusion of 3 percent sodium chloride, and the intravenous administration of 20 mg of furosemide. The estimated volume of total body water is 36 liters (0.60×60).

According to formula 1 of Table 2, the retention of 1 liter of 3 percent sodium chloride is estimated to increase the serum sodium concentration by 10.9 mmol per liter ($[513-108] \div [36+1] = 10.9$). The initial goal is to increase the serum sodium concentration by 5 mmol per liter over the next 12 hours. Therefore, 0.46 liter of 3 percent sodium chloride ($5 \div 10.9$), or 38 ml per hour, is required.

Twelve hours after admission, the serum sodium concentration is 114 mmol per liter. The patient is mildly lethargic but easily arousable. Hypertonic saline is stopped, but fluid restriction and close monitoring continue. The new goal is to increase the serum sodium concentration by 2 mmol per liter over the next 12 hours. Twenty-four hours after admission, the serum sodium concentration is 115 mmol per liter and the patient is alert. Long-term management of hyponatremia is instituted.

Hyponatremia in a Hypovolemic State

A 68-year-old woman is brought to the hospital because of progressive drowsiness and syncope. She is being treated with a low-sodium diet and 25 mg of hydrochlorothiazide daily for essential hypertension; she has had diarrhea for the past three days. She is lethargic but has no focal neurologic deficits. She weighs 60 kg. Her blood pressure while in a supine position is 96/56 mm Hg, and the pulse is 110 beats per minute. The jugular veins are flat, and skin turgor is decreased. The serum sodium concentration is 106 mmol per liter, the serum potassium concentration is 2.2 mmol per liter, the serum bicarbonate concentration is 26 mmol per liter, the serum urea nitrogen concentration is 46 mg per deciliter (16.4 mmol per liter), the serum creatinine concentration is 1.4 mg per deciliter (123.8 μmol per liter), serum osmolality is 232 mOsm per kilogram of water, and urine osmolality is 650 mOsm per kilogram of water. Hypotonic hyponatremia caused by thiazide therapy, gastrointestinal losses of sodium, and an associated depletion of potassium are diagnosed. Hydrochlorothiazide and water are withheld, and infusion of a 0.9 percent sodium chloride solution containing 30 mmol of potassium chloride per liter is initiated. The estimated volume of total body water is 27 liters (0.45×60).

According to formula 2 of Table 2 (a simple derivative of formula 1), it is projected that the retention of 1 liter of this infusate will increase the serum sodium concentration by 2.8 mmol per liter ($[154+30] - 106 \div [27+1] = 2.8$). Considering the patient's hemodynamic status, the physician prescribes 1 liter of infusate per hour for the next two hours. At the end of this period, the blood pressure is 128/72 mm Hg, mental status is substantially improved, the serum sodium concentration is 112 mmol per liter, and the serum potassium concentration is 3.0 mmol per liter. The physician recognizes that as soon as the patient's extracellular-fluid volume nears restoration, the nonosmotic stimulus to arginine vasopressin release will cease, thereby fostering rapid excretion of dilute urine and correction of the hyponatremia at an overly rapid pace. Therefore, the prescription is switched to 0.45 percent sodium chloride containing 30 mmol of potassium chloride per liter infused at 100 ml per hour. Despite the estimate that retention of 1 liter of this infusate will have no measurable effect on the serum sodium concentration (i.e., $[77+30] - 112 \div [27+1] = -0.2$), the anticipated production of urine with lower sodium and potassium concentrations than those of the infusate will promote correc-

tion of the hyponatremia. Twelve hours after admission, the patient's condition continues to improve; the serum sodium concentration is 114 mmol per liter, and the serum potassium concentration is 3.2 mmol per liter. To slow down further correction over the next 12 hours, an infusion of 5 percent dextrose in water containing 30 mmol of potassium chloride per liter is started at a rate matching urinary output. Subsequently, long-term management of hyponatremia should be pursued.

Asymptomatic Hypotonic Hyponatremia

For certain patients with asymptomatic hyponatremia, the main risk of complications occurs during the correction phase. This is true of patients who stopped drinking large amounts of water[36] and those who underwent repair of a water-excretion defect (e.g., repletion of extracellular-fluid volume and discontinuation of drugs that cause the condition). If excessive diuresis occurs and the projected rate of spontaneous correction exceeds that recommended for patients with symptomatic hyponatremia, hypotonic fluids or desmopressin can be administered.[44]

By contrast, there is no such risk associated with the asymptomatic hyponatremia that accompanies edematous states or the persistent syndrome of inappropriate secretion of antidiuretic hormone because of the prevailing defect of water excretion. Water restriction (to <800 ml per day) is the mainstay of long-term management, with the goal being induction of negative water balance.[43,44] In severe cardiac failure, optimization of hemodynamics by several measures, including the use of angiotensin-converting–enzyme inhibitors, can increase excretion of electrolyte-free water and moderate hyponatremia. Loop, but not thiazide, diuretics reduce urine concentration and augment excretion of electrolyte-free water, thereby permitting relaxation of fluid restriction. In the syndrome of inappropriate secretion of antidiuretic hormone, but not in edematous disorders, loop diuretics should be combined with plentiful sodium intake (in the form of dietary sodium or salt tablets), a treatment that augments water loss. If these measures fail, 600 to 1200 mg of demeclocycline per day can help by inducing nephrogenic diabetes insipidus.[44] Monitoring of renal function is required, because demeclocycline has nephrotoxic effects, especially in patients with cirrhosis. Moreover, the drug imposes the risk of hypernatremia in patients who do not take in sufficient water. Management of chronic hyponatremia will be helped by the anticipated introduction of promising oral agents that antagonize the effect of arginine vasopressin on the V_2 receptor.[59,60]

Nonhypotonic Hyponatremia

Corrective measures for nonhypotonic hyponatremia are directed at the underlying disorder rather than at the hyponatremia itself. Administration of insulin is the basis of treatment for uncontrolled diabetes, but deficits of water, sodium, and potassium should also be corrected. Furosemide hastens the recovery of patients who absorb irrigant solutions; if renal function is impaired, hemodialysis is the preferred option.[22]

Common Errors in Management

Although water restriction will ameliorate all forms of hyponatremia, it is not the optimal therapy in all cases. Hyponatremias associated with the depletion of extracellular-fluid volume (Table 1) require correction of the prevailing sodium deficit. On the other hand, isotonic saline is unsuitable for correcting the hyponatremia of the syndrome of inappropriate secretion of antidiuretic hormone; if administered, the resulting rise in serum sodium is both small and transient, with the infused salt being excreted in concentrated urine and thereby causing a net retention of water and worsening of the hyponatremia.[38] Although uncertainty about the diagnosis might occasionally justify a limited trial of isotonic saline, attentive follow-up is needed to confirm the diagnosis before substantial deterioration occurs. Great vigilance is required in order to recognize and diagnose hypothyroidism and adrenal insufficiency, since these disorders tend to masquerade as cases of the syndrome of inappropriate secretion of antidiuretic hormone. The presence of hyperkalemia should always alert the physician to the possibility of adrenal insufficiency.

Whereas patients with persistent asymptomatic hyponatremia require slow-paced management, those with symptomatic hyponatremia must receive rapid but controlled correction. Prudent use of hypertonic saline can be lifesaving, but failure to follow the recommendations for treatment can cause devastating and even lethal consequences.

Hyponatremia that is acquired in the hospital is largely preventable.[6] A defect of water excretion can be present on admission, or it can worsen or develop during the course of hospitalization as a result of several antidiuretic influences (e.g., medications, organ failure, and the postoperative state). The presence of such a defect notwithstanding, hyponatremia will not develop as long as the intake of electrolyte-free water does not exceed the capacity for water excretion plus insensible losses. Thus, hypotonic fluids must be supplied carefully to hospitalized patients.

We are indebted to Linda Sue Seals and Yulie I. Tirayoh for assistance in the preparation of the manuscript.

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Nephrol Dial Transplant (2006) 21: 1564–1569
doi:10.1093/ndt/gfk090
Advance Access publication 31 January 2006

Original Article

NDT
Nephrology Dialysis Transplantation

Therapeutic approach in patients with dysnatraemias

George Liamis, Michalis Kalogirou, Vasilios Saugos and Moses Elisaf

Department of Internal Medicine, Medical School, University of Ioannina, 45110 Ioannina, Greece

Abstract

Background. Rapid correction of dysnatraemias is frequently associated with increased morbidity and mortality. Therefore, it is important to estimate the proper volume and type of infusate required to change the serum sodium concentration predictably. The aim of this study is to evaluate the utility or/and the accuracy of the Adrogue–Madias formula in managing patients with hyponatraemia and hypernatraemia.

Methods. Among the 317 patients who either on admission to our internal medicine clinic or during their hospitalization were found to have hyponatraemia or hypernatraemia, we studied 189 patients (59.6%) in whom the administration of intravenous solutions was required for the correction of dysnatraemias.

Results. Twelve hours after starting the administration of intravenous solutions the anticipated as well as the achieved serum sodium concentration were as follows: in volume depleted patients 130.2 ± 4.1 *vs* 131.3 ± 5.2 meq/l ($n = 45$; $P =$ NS), in syndrome of inappropriate antidiuretic hormone secretion (SIADH) patients 127.4 ± 5.7 *vs* 128.9 ± 5.9 meq/l ($n = 10$; $P =$ NS), in patients with diuretic-induced hyponatraemia 123.8 ± 6 *vs* 125.5 ± 5.6 meq/l ($n = 29$; $P =$ NS), in patients with primary polydipsia 122.5 ± 0.7 *vs* 129 ± 1.4 meq/l ($n = 2$; $P = 0.02$), while in patients with hypernatraemia 153.6 ± 7.5 *vs* 156.5 ± 8.9 meq/l ($n = 92$; $P = 0.021$). Furthermore, 24 h from the initiation of the therapeutic intervention the expected and the achieved serum sodium concentrations were 130 ± 4 *vs* 135.6 ± 3.3 meq/l ($n = 15$; $P = 0.002$) in patients with volume depletion, 128.1 ± 4.8 *vs* 130 ± 4.5 meq/l ($n = 15$; $P =$ NS) in patients with diuretic-induced hyponatraemia and 151.5 ± 6.4 *vs* 153.3 ± 8.3 meq/l ($n = 67$; $P =$ NS) in patients with hypernatraemia.

Conclusions. The formula that has been proposed by Adrogue and Madias predicted with relative accuracy the changes in serum sodium concentration in almost all patients. Thus, it should be considered as a very useful tool for the management of dysnatraemias. However, special attention should be paid when this equation is used in patients with hyponatraemia due to extracellular volume depletion after euvolaemia's restoration and primary polydipsia in order to avoid rapid correction of hyponatraemia.

Keywords: adrogue–madias formula; hypernatraemia; hyponatraemia

Introduction

Dysnatraemias are frequent electrolyte abnormalities occurring in a broad spectrum of patients. Such patients are exposed to major neurologic complications [1–3]. Hyponatraemia and hypernatraemia produce brain oedema and dehydration, respectively, which potentially lead to subsequent neuropathological sequalae or death. On the other hand, rapid correction of dysnatraemias is associated with increased morbidity and mortality. Specifically, excessive treatment for hyponatraemia could be followed by development of central demyelinating lesions, particularly in the pons (a disorder called central pontine myelinolysis or osmotic demyelination) with major disability or even fatal outcome [4–9]. Likewise, overcorrection of hypernatraemia can induce cerebral oedema, seizures, permanent neurologic damage and death [10–11]. So, the treatment for hyponatraemia/hypernatraemia is focused mainly on how to avoid the devastating neurologic complications, which can potentially occur either during the course of untreated dysnatraemias or after inappropriate correction of these disorders. Consequently, formulas that accurately predict the change in serum sodium concentration as a result of a given course of therapy are of paramount importance. Recently, Adrogue and Madias proposed a new formula for the management of both hyponatraemia and hypernatraemia [12–14]. According to this formula, the anticipated change in the patient's serum sodium concentration as a result of administration of 1 l of any

Correspondence and offprint requests to: Moses Elisaf, MD, FRSH, FASA, Professor of Medicine, Department of Internal Medicine, University of Ioannina, 45110 Ioannina. Email: egepi@cc.uoi.gr

infusate can be calculated by equation (1):

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

where $\Delta[Na^+]$, $[Na^+]_{inf}$ and $[Na^+]_s$ represent the expected change in the patient's serum sodium concentration, the sodium concentration of the infusate and the sodium concentration of the patient's serum, respectively, expressed in meq/l, and TBW represents the patient's estimated total body water, expressed in litres. When the administered solution contains potassium chloride also, the equation (1) is converted as follows:

$$\Delta[Na^+] = \{([Na^+]_{inf} + [K^+]_{inf}) - [Na^+]_s\}/(TBW + 1) \quad (2)$$

where $[K^+]_{inf}$ represent the potassium concentration of the infusate.

However, the precision of this equation has not been verified in large series of patients with dysnatraemias of various origins. The aim of this prospective study was the evaluation of the utility or/and the accuracy of the Adrogue–Madias formula for the proper management of patients with hyponatraemia and hypernatraemia.

Patients and methods

Over a period of 2.5 years (starting on 5 February 1999), we studied prospectively non-selected, consecutive, adult patients (over 14 years of age) who either on admission to our clinic or during their hospitalization were found to have hyponatraemia or hypernatraemia. The study took place in the internal medicine clinic (60 beds) at the University Hospital of Ioannina (600 beds). To be eligible, patients had to have had a serum sodium concentration ($[Na^+]$) less than 130 meq/l or more than 148 meq/l that was verified by a repeat measurement to exclude laboratory error. In hyperglycaemic patients, the corrected serum sodium concentration was evaluated. In this setting, the corrected $[Na^+]$ was calculated by increasing $[Na^+]$ by 1.6 meq/l for every 100 mg/dl increment in the serum glucose above normal, while the correction factor 2.4 meq/l was used for serum glucose concentration >400 mg/dl [15]. Patients with corrected >130 meq/l or <149 meq/l were excluded from the study. In all cases, a detailed history was obtained, while each patient underwent a complete physical examination with special attention to orthostatic changes in the pulse rate and blood pressure, jugular venous pressure, skin turgour, moisture in the axillae and hydration of mucous membranes. Orthostatic hypotension and orthostatic change in pulse rate were defined as a reduction in systolic blood pressure of at least 20 mmHg and an increase in pulse rate of at least 10% after 2 min in the upright position compared with the supine position, respectively. Furthermore, special attention was paid to determine the duration as well as the presence of symptoms of the dysnatraemias. Prior to any therapeutic intervention, venous blood was obtained for the determination of serum glucose, urea, creatinine, uric acid, sodium, potassium, chloride, calcium, magnesium, phosphorus, triglycerides, osmolality (P_{osm}), cortisol and thyroid-stimulating hormone (TSH). Also, a fresh urine specimen was tested for osmolality (U_{osm}), creatinine and sodium. A standard formula was used for the determination of the fractional excretion of sodium ($FENa^+$).

In hyponatraemic patients, the detection of the cause of hyponatraemia was one of our primary tasks. The diagnostic approach was based on history, physical examination and laboratory tests. In particular, diuretic-induced hyponatraemia was defined as hyponatraemia in patients receiving diuretics but in the absence of heart failure, hepatic cirrhosis, nephrotic syndrome, extracellular volume depletion unrelated to diuretics, renal insufficiency unrelated to diuretics and SIADH.

Hyponatraemia due to extracellular volume depletion was diagnosed in patients with historical (e.g. vomiting, diarrhoea), clinical (such as postural changes in blood pressure and pulse rate, decreased skin turgour or axillary moisture and dry mucous membranes) or/and laboratory (serum urea to creatinine ratio greater than 40, urine sodium less than 20 meq/l and $FENa^+$ <1%) indications of hypovolaemia. The diagnosis of the syndrome of inappropriate antidiuretic hormone (ADH) secretion was made in patients who fulfilled the following criteria: (1) hyponatraemia and hypoosmolality; (2) increased U_{osm} (greater than 100 mosmol/kg); (3) inappropriate natriuresis (greater than 40 meq/l); (4) normovolaemia; (5) normal renal, adrenal and thyroid function and (6) normal acid-base and potassium balance [16]. The diagnosis of SIADH was also supported by the presence of hypouricaemia, as well as by low serum urea and phosphate levels, if present.

This report is focused on patients who received intravenous solutions for the correction of dysnatraemias. The decision to treat patients with or without infusions, as well as the determination of the rate of correction was based on the presence of symptoms directly attributed to dysnatraemias, the degree of dysnatraemias, whether the condition is acute (defined as a duration of less than 48 h) or chronic, and the presence of hypovolaemia. Given their diverse and nonspecific nature, the symptoms of both hyponatraemia (headache, nausea, vomiting, muscle cramps, restlessness, followed by disorientation, seizures, respiratory arrest and coma) and hypernatraemia (lethargy, weakness, irritability, seizures and coma) were ascribed to dysnatraemias after excluding other possible causes. In fact, only patients with symptomatic dysnatraemias or/and patients with extracellular volume depletion participated in this study. In these patients, the serum as well as the anticipated (based on Adrogué–Madias formula) sodium concentration was determined at 12, 24 and 36 h after starting the infusion.

Patients with acute, severely symptomatic hyponatraemia (e.g. seizures) were treated in an aggressive but controlled fashion (1.5–2 meq/l/h for 3–4 h or until the severe neurologic symptoms were alleviated), while less symptomatic hyponatraemia was corrected at a slow pace (<0.5 meq/l/h). However, in all patients our therapeutic target was to limit the increase in the serum sodium concentration to less than 12 meq/l on the first day and to less than 18 meq/l in the first 2 days of treatment, as well as to avoid the overcorrection of the serum sodium concentration to above 140 meq/l within the first 2 days of treatment. The cessation of hyponatraemic symptoms and the euvolaemia's restoration led us to stop the intravenous solutions. In patients with symptomatic hypernatraemia that was developed over a period of less

than 48 h, a rapid correction of serum sodium concentration (1–2 meq/l/h) was initially performed, while a slower rate of serum sodium reduction (<0.5 meq/l/h) was attained in patients with hypernatraemia of longer or unknown duration. In all patients, though, the targeted fall in the serum sodium concentration was up to 12 meq/l per day. Finally, the goal of treatment was to reduce the serum sodium concentration to 145 meq/l. When the patients were able to take fluids orally the intravenous solutions were stopped.

Laboratory determinations were carried out by automated chemical analysis in our laboratory using an Olympus AU 600 analyser (Olympus Diagnostica, Hamburg, Germany). Specifically, urine and serum samples were analysed using ion-sensitive electrodes for sodium, potassium and calcium, and photometric assays for phosphorus and magnesium. The glutamate dehydrogenase method was used for determining urea levels and a modification of the Jaffé method for creatinine measurement. The hexokinase and uricase methods were used for determining glucose and uric acid levels, respectively. Serum triglycerides were determined by enzymatic colorimetric assay. TSH was measured by microparticle enzyme immunoassay (ABBOTT GmbH Diagnostika, Wiesbaden-Delkenheim, Germany) and serum cortisol by competitive immunoassay (competitive ELISA, Immulite, DPC, Los Angeles, CA, USA). Serum and urine osmolality was assayed using a vapour pressure osmometer.

The TBW was estimated as 60 and 50% of lean body weight in men and women, respectively. In water-depleted hypernatraemic patients, we used lower values (50% of lean body weight in men and 40% in women).

The ethics and science committee of our hospital approved the study protocol.

Statistical analysis

The results were expressed as mean ± SD. The comparison of laboratory parameters among groups was performed by one way analysis of variance (ANOVA) followed by the LSD test for paired comparison. *P*-values less than 0.05 were considered to indicate statistical significance.

Results

317 patients fulfilled the inclusion criterion of the serum sodium concentration. 204 patients had hyponatraemia, while 117 exhibited hypernatraemia. In 189 patients (59.6%), the administration of intravenous solutions was required for the correction of dysnatraemias.

The major causes of hyponatraemia were as follows: syndrome of inappropriate ADH secretion ($n = 55$), extracellular volume depletion ($n = 53$), diuretic administration ($n = 40$), hepatic cirrhosis ($n = 22$), heart failure ($n = 9$) and primary polydipsia ($n = 4$). The laboratory data in patients with the three most frequent causes of hyponatraemia (SIADH, extracellular volume depletion and diuretics) are shown in Table 1. Patients with hyponatraemia due to SIADH had lower serum concentrations of uric acid, phosphorus, urea and creatinine, and urea/creatinine ratio, but higher $FENa^+$ than patients with extracellular volume depletion. Compared with hyponatraemic patients due to hypovolaemia and SIADH, patients with diuretic-induced hyponatraemia had lower serum concentrations of sodium, potassium, chloride and magnesium, as well as higher serum concentrations of calcium. Also, they exhibited higher $FENa^+$ (Table 1).

In patients with volume depletion (baseline serum sodium concentration 128.3 ± 3.7 meq/l), 12 h after starting the administration of intravenous solutions, the expected, based on the Adrogue–Madias formula,

Table 1. Laboratory characteristics in patients with hyponatraemia due to diuretics, hypovolaemia and SIADH

Parameter	Diuretics ($n = 40$) Mean ± SD	Hypovolaemia ($n = 53$) Mean ± SD	SIADH ($n = 55$) Mean ± SD	*P*-value
Serum				
Sodium (meq/l)	121.7 ± 7.5	128.4 ± 4.7§§	126.7 ± 6.3§§	0.0000
Potassium (meq/l)	3.8 ± 0.7	4.3 ± 0.7§	4.2 ± 0.6§	0.01
Chloride (meq/l)	85 ± 9.4	94 ± 6.4§§	91 ± 7.4§	0.0001
Phosphorus (mg/dl)	3 ± 0.6	3.5 ± 0.9§	2.8 ± 0.6**	0.003
Magnesium (meq/l)	1.3 ± 0.2	1.5 ± 0.3§	1.5 ± 0.2§	0.01
Uric acid (mg/dl)	5.5 ± 2.7	6.6 ± 2.9	3 ± 1.1**,§§	0.000
Calcium (mg/dl)	9.3 ± 0.8	8.4 ± 0.8§§	8.5 ± 0.6§§	0.000
Urea (mg/dl)	50.3 ± 40	84.6 ± 63.9§	25.6 ± 12.5**,§	0.000
Creatinine (mg/dl)	1.1 ± 0.4	1.4 ± 0.6§	0.8 ± 0.1**,§	0.000
Urea/Creatinine	43.1 ± 21.4	60 ± 30§	31 ± 11**,§	0.000
Osmolality (mosmol/kg)	259 ± 18.2	280.6 ± 14.3§§	265 ± 13.6**	0.0000
Arterial blood gases				
pH	7.47 ± 0.04	7.45 ± 0.07	7.46 ± 0.04	NS
HCO_3^- (meq/l)	26.1 ± 4.1	22.8 ± 5§	24.9 ± 4	0.02
PCO_2 (mmHg)	35 ± 4.7	32.1 ± 8.4	34 ± 5	NS
Urine				
Fractional excretion of Sodium (%)	1.3 ± 1	0.4 ± 0.2§§	0.8 ± 0.5*,§	0.000

*$P < 0.05$ compared to hypovolaemia.
**$P < 0.001$ compared to hypovolaemia.
$^{\S}P < 0.05$ compared to diuretics.
$^{\S\S}P < 0.001$ compared to diuretics.

serum sodium concentration was 130.2 ± 4.1 meq/l, while the achieved serum sodium concentration was 131.3 ± 5.2 meq/l ($n = 45$; P = NS). 24 h from the initiation of the therapeutic intervention the anticipated serum sodium concentration was 130 ± 4 meq/l, whereas the achieved serum sodium concentration was 135.6 ± 3.3 meq/l ($n = 15$; $P = 0.002$). Finally, after 36 h the expected as well as the achieved serum sodium values were 135.5 ± 3.8 and 136.8 ± 4.3 meq/l, respectively ($n = 6$; P = NS). In all these cases, normal saline ± potassium chloride was administered intravenously to correct the hypovolaemia and the hypokalaemia, if present. The mean volume of administered infusate per each successive 12 h interval of intravenous therapy was 1.3 ± 0.4, 1.2 ± 0.3 and 1 ± 0.2 l, respectively. Finally, electrolyte-free water intake was restricted to 0.5–1 l/day.

In symptomatic hyponatraemic patients due to SIADH (baseline serum sodium concentration 122.6 ± 5.1 meq/l, $n = 10$), hypertonic saline (3N) with furosemide was administered, while water restriction to less than 500–750 ml/day was prescribed. The coadministration of a loop diuretic enhances solute-free water excretion, while the possible circulatory overload is prevented. In these patients, 12 h after initiating the infusion of hypertonic solution, the expected serum sodium concentration was 127.4 ± 5.7 meq/l, while the achieved serum sodium concentration was 128.9 ± 5.9 meq/l (P = NS). 24 h after starting the administration of intravenous solutions, the expected serum sodium concentration was 129.4 ± 6.3 meq/l, while the achieved serum sodium concentration was 131.4 ± 6.4 meq/l ($n = 4$; P = NS). The mean volume of hypertonic solution per 12 h of intravenous therapy was 310 ± 20 and 250 ± 50 ml, respectively.

In patients with diuretic-induced hyponatraemia (baseline serum sodium concentration 120.7 ± 7.6 meq/l), 12 h from the beginning of the administration of intravenous solutions, the anticipated serum sodium concentration was 123.8 ± 6 meq/l, while the achieved serum sodium concentration was 125.5 ± 5.6 meq/l ($n = 31$; P = NS). 24 h after starting the administration of intravenous solutions, the expected serum sodium concentration was 125.2 ± 5.1 meq/l, while the achieved serum sodium concentration was 127.3 ± 6.1 meq/l ($n = 15$; P = NS). Finally, after 36 h the expected as well as the achieved serum sodium values were 129.3 ± 4.9 and 132.1 ± 5.3 meq/l, respectively ($n = 8$; P = NS). It should be noticed that there were two subgroups of patients with diuretic-induced hyponatraemia, one with extracellular volume depletion and another with euvolaemic state. Patients with normovolaemic hyponatraemia had lower serum concentrations of urea (28.4 ± 8.6 *vs* 68.2 ± 47.2 mg/dl, $P = 0.005$), creatinine (0.8 ± 0.1 *vs* 1.27 ± 0.5 mg/dl, $P = 0.003$), uric acid (2.7 ± 0.8 *vs* 7.2 ± 1.9 mg/dl, $P = 0.001$) and urea/creatinine ratio (34.1 ± 7.3 *vs* 51.6 ± 25.5, $P = 0.017$) than patients with hypovolaemic hyponatraemia due to diuretics. All patients were receiving thiazide or thiazide-like agents, while there were no differences between the two subgroups in age, gender distribution, or diuretic dose. In all patients, diuretic administration was withheld, whereas all patients who reported increased water intake ($n = 23$) were placed on water restriction (<500–750 ml/day). In patients with extracellular volume depletion ($n = 25$), normal saline ± potassium chloride was administered intravenously to correct the hypovolaemia and the hypokalaemia, if present. In patients with euvolaemic symptomatic hyponatraemia ($n = 6$), hypertonic sodium chloride solution (3N) was administered intravenously and water was withheld to less than 500–750 ml/day. In the extracellular volume depletion subgroup, the mean volume of administered infusate (normal saline ± potassium chloride) per each successive 12 h interval of intravenous therapy was 1.2 ± 0.3, 1.05 ± 0.2 and 0.95 ± 0.1 l, respectively. In the euvolaemic subgroup, the corresponding mean volume of administered infusate (hypertonic saline) was 315 ± 25, 260 ± 55 and 240 ± 40 ml, respectively. It should be emphasized that there were no statistically significant differences between anticipated and achieved serum sodium values in the two subgroups of patients with diuretic-induced hyponatraemia (data submitted for publication).

In two patients with symptomatic hyponatraemia due to primary polydipsia (admission serum sodium concentration: 116 ± 4.2 meq/l), 12 h after initiating the infusion of hypertonic solution the expected serum sodium concentration was 122.5 ± 0.7 meq/l, while the achieved serum sodium concentration was 127.8 ± 1.4 meq/l ($P = 0.02$). The mean volume of administered hypertonic solution was 350 ± 20 ml. Over the treatment, these patients were also placed on water restriction (less than 500–750 ml/day).

117 patients exhibited hypernatraemia. 52 were hypernatraemic on hospital admission and 65 developed hypernatraemia during hospitalization. In the vast majority of hypernatraemic patients, more than one condition contributed to the development of hypernatraemia; the most common factors were: febrile illnesses (72%; mainly pulmonary infections), uncontrolled diabetes mellitus (30%), mannitol (21%) or diuretics (10%; mainly furosemide) administration, gastrointestinal losses (10%) and environment's high temperature (30%). Additionally, in almost all cases (91%) the water intake was markedly diminished because of the patients' altered mental status. In patients with hypernatraemia (baseline serum sodium concentration 157.8 ± 8.8 meq/l), 12 h from the beginning of the administration of intravenous solutions, the anticipated as well as the achieved serum sodium concentrations were 153.6 ± 7.5 and 156.5 ± 8.9 meq/l, respectively ($n = 92$; $P = 0.021$). There was, however, a subgroup of eight patients (8.7%) in whom a considerable disparity between the anticipated and achieved serum sodium concentration was observed over the first 12 h of treatment (152.2 ± 5.8 *vs* 161 ± 4.8 meq/l, $P = 0.003$). These patients had higher serum concentrations of urea (290 ± 109.6 *vs* 113.4 ± 48.3 mg/dl, $P = 0.000$) and creatinine (3.3 ± 1 *vs* 1.7 ± 0.8 mg/dl, $P = 0.000$), whereas they exhibited lower serum sodium

concentration (155.1 ± 7.3 *vs* 157.8 ± 8.9 meq/l, $P = 0.135$) as compared to the rest of hypernatraemic patients. Infact, in these cases an increase in the serum sodium concentration was initially found contrary to the expected decrement. On the other hand, a simultaneous reduction in the serum concentration of urea (243.5 ± 96 *vs* 290.4 ± 109.6 mg/dl, $P = 0.4$) and creatinine (2.5 ± 0.9 *vs* 3.3 ± 1 mg/dl, $P = 0.18$) was observed. It should be mentioned that these patients' haemodynamic status was sufficiently compromised, consequently normal saline was initially administered intravenously to correct the hypovolaemia. Not including this subgroup of patients, there were no statistically significant differences between the anticipated and the achieved serum sodium concentration in the remaining hypernatraemic patients (153.1 ± 7.2 *vs* 154.3 ± 7.8). Furthermore, 24 h from the initiation of the therapeutic intervention in the whole group of patients ($n = 67$) the anticipated serum sodium concentration was 151.5 ± 6.4, whereas the achieved serum sodium concentration was 153.3 ± 8.3 meq/l ($P = 0.15$). Finally, after 36 h the expected as well as the achieved serum sodium concentration was 149 ± 6.2 and 150 ± 6.8 meq/l, respectively ($n = 34$; $P = 0.28$). It is of interest that a considerable percentage of the hypernatraemic patients had clinical findings (such as postural changes in blood pressure and pulse rate, decreased skin turgour or axillary moisture and dry mucous membranes) and laboratory evidence (serum urea to creatinine ratio greater than 40, urine sodium less than 20 meq/l and $FENa^+$ <1%) of extracellular volume depletion. Based on both the patients' clinical state and laboratory findings, 71 subjects (62.8%) exhibited hypovolaemic hypernatraemia. Except for the previously mentioned eight patients with severe hypovolaemia (who were treated initially with isotonic saline) all the remaining hypovolaemic patients received half-isotonic ($n = 22$) or quarter-isotonic saline ($n = 41$). The mean volume of administered infusate per each successive 12 h interval of intravenous therapy was 2.2 ± 0.4, 1.8 ± 0.3 and 1.5 ± 0.2 l, respectively. In contrast, hypernatraemia due to pure water loss was found in 36 patients (31.8%). Of those, 24 patients received free water intravenously, while the remaining orally. The mean volume of administered infusate (as dextrose 5% in water) per each consecutive 12 h interval of intravenous treatment was 1.8 ± 0.4, 1.5 ± 0.3 and 1.3 ± 0.2 l, respectively.

The expected as well as the achieved serum sodium concentrations are summarized in Table 2.

Table 2. Anticipated and achieved serum sodium concentration at 12, 24 and 36 h after starting the infusion of intravenous solution for treatment in patients with dysnatraemias

	Anticipated serum Na^+ concentration (meq/l)	Achieved serum Na^+ concentration (meq/l)	*P*-value
Volume depletion			
12 h ($n = 45$)	130.2 ± 4.1	131.3 ± 5.2	NS
24 h ($n = 15$)	130 ± 4	135.6 ± 3.3	0.002
36 h ($n = 6$)	135.5 ± 3.8	136.8 ± 4.3	NS
SIADH			
12 h ($n = 10$)	127.4 ± 5.7	128.9 ± 5.9	NS
24 h ($n = 4$)	129.4 ± 6.3	131.4 ± 6.4	NS
Diuretics			
12 h ($n = 29$)	123.8 ± 6	125.5 ± 5.6	NS
24 h ($n = 15$)	125.2 ± 5.1	127.3 ± 6.1	NS
36 h ($n = 8$)	129.3 ± 4.9	132.1 ± 5.3	NS
Primary polydipsia			
12 ($n = 2$)	122.5 ± 0.7	127.8 ± 1.4	0.02
Hypernatraemia			
12 h ($n = 92$)	153.6 ± 7.5	156.5 ± 8.9	0.021
24 h ($n = 67$)	151.5 ± 6.4	153.3 ± 8.3	NS
36 h ($n = 34$)	149 ± 6.2	150.7 ± 6.8	NS

Discussion

The present study, for the first time in the literature, provides an external validation of the formula proposed by Adrogue and Madias in prescribing fluid therapy for patients with dysnatraemias [13–15].

This study showed that the Adrogue–Madias formula predicted with relative accuracy the changes of the serum sodium concentration in patients with diuretic-induced hyponatraemia, SIADH patients, volume depleted patients (before euvolaemia's restoration) as well as in the majority of hypernatraemic patients. Indeed, in these cases, there were no statistically significant differences between anticipated and achieved values of serum sodium concentration, thus supporting the clinical utility of the formula. This favourable assessment is noticeable taking into consideration that the formula's output depends on a reliable estimate of TBW (equation1); yet the clinical estimate of TBW is a rough approximation at best. It is noteworthy, however, that the mean serum sodium values anticipated by the formula were consistently somewhat lower (by 1–3 meq/l) than those achieved. This disparity should be attributed to the fact that the Adrogue–Madias formula considers the patient as a closed system, not taking into account any ongoing urinary, dermal and respiratory fluid losses. As the sum of the sodium and potassium concentrations in these fluid losses is lower than that of serum, these losses would contribute to the increase in serum sodium values. Finally, despite the lack of statistical significance between anticipated and achieved serum sodium values, there were some cases in which a considerable aberration (>4 meq/l) between the anticipated and achieved serum sodium concentration was observed. Therefore, serial measurements of the serum sodium values are required to ascertain that the desired rate of correction is being achieved.

Nevertheless, the expected, based on the Adrogue–Madias formula, serum sodium values were statistically significant lower than those achieved in cases of hyponatraemia due to extracellular volume depletion (at 24 h after starting the infusion of intravenous solution) and primary polydipsia. In fact, the Adrogue–Madias equation underestimates the increment of the serum sodium concentration in patients

with polydipsia or volume depletion after water restriction or euvolaemia's restoration, respectively. In each of these conditions, ADH release is appropriately suppressed, thereby allowing the excess water to be rapidly excreted in a dilute urine and correction of the hyponatraemia at an overly rapid pace.

Moreover, the formula was unable to predict correctly the serum sodium concentration changes in a subgroup of patients with hypernatraemia and severe extracellular volume depletion as well as marked reduction of renal function. In these cases, in spite of administering relatively hypotonic solutions as compared to patients' serum, an increase in the serum sodium concentration was initially observed, while the renal function was improved. This increment of the serum sodium values can be attributed to the fact that the administered solutions were relatively hypertonic compared with the ongoing hypotonic fluid losses, which are not taken into consideration by the Adrogue–Madias equation.

The sodium deficit equation as well as the water deficit equation are frequently utilized for guiding treatment of hyponatraemia and hypernatraemia, respectively [17,18]. However, there are several limitations regarding the use of these formulas [19]. For example, the water deficit equation is only applicable in patients with hypernatraemia caused by pure water loss without concomitant Na^+ loss. Our study, on the contrary, clearly showed that the majority of hypernatraemic patients (62.8%) exhibited hypovolaemic hypernatraemia. Consequently, the Adrogue–Madias formula both being applicable to the treatment of hyponatraemia and hypernatraemia of any origin and guiding the physician as regards the composition or the infusion rate of anyone of the infusates excels in managing patients with dysnatraemias as compared to the sodium deficit equation as well as the water deficit equation. Furthermore, its simplicity is the main advantage in comparison with two novel formulas proposed by Nguyen and Kurtz as well as Barsoum and Levine, respectively [19,20]. It should be emphasized, however, that our study was not designed to compare the Adrogue–Madias equation with the other equations.

In conclusion, our study clearly showed that the Adrogue–Madias formula predicted with relative accuracy the changes in serum sodium concentration in the majority of patients. Thus, it should be considered as a very useful tool for the management of dysnatraemias. However, caution is warranted in prescribing therapy, since the formula-based quantitative projections tend to underestimate the mark. Moreover, extra attention should be paid and serial measurements of the serum sodium concentration are required when this equation is used, especially in patients with hyponatraemia due to extracellular volume depletion after euvolaemia's restoration and primary polydipsia as well as in patients with hypernatraemia and severe hypovolaemia in order to avoid rapid correction of hyponatraemia and deterioration of hypernatraemia, respectively.

Conflict of interest statement. None declared.

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Received for publication: 29.8.05
Accepted in revised form: 3.1.06

Hypertonic Saline for Hyponatremia: Risk of Inadvertent Overcorrection

Hashim K. Mohmand,* Dany Issa,† Zubair Ahmad,‡ Joseph D. Cappuccio,‡ Ruth W. Kouides,‡ and Richard H. Sterns‡

**Department of Medicine, University of Cincinnati Medical Center, Cincinnati, Ohio; †Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; and ‡Department of Medicine, Rochester General Hospital, Rochester, New York*

Background and objectives: Data regarding dosage–response relationships for using hypertonic saline in treatment of hyponatremia are extremely limited. Objectives of this study were to assess adherence to previously published guidelines (limiting correction to <12 mEq/L per d and <18 mEq/L per 48 h) in treating hyponatremia with hypertonic saline and to determine the predictive accuracy of the Adrogué-Madias formula.

Design, setting, participants & measurements: A retrospective review was conducted of all 62 adult, hyponatremic patients who were treated with hypertonic saline during 5 yr at a 528-bed, acute care, teaching hospital.

Results: Median infusion rate was 0.38 ml/kg per h, increasing serum sodium concentration by 0.47 ± 0.05 mEq/L per h, 7.1 ± 0.6 mEq/L per 24 h, and 11.3 ± 0.7 mEq/L per 48 h. In 11.3% of cases, the increase was >12 mEq/L per 24 h and in 9.7% was >18 mEq/L per 48 h. No patient's rate was corrected by >25 mEq/L per 48 h. Among patients with serum sodium <120 mEq/L, the observed increase in sodium exceeded the rise predicted by the Adrogué-Madias formula in 74.2%; the average correction in overcorrectors was 2.4 times the predicted. Inadvertent overcorrection was due to documented water diuresis in 40% of cases.

Conclusions: The Adrogué-Madias formula underestimates increase in sodium concentration after hypertonic saline therapy. Unrecognized hypovolemia and other reversible causes of water retention pose a risk for inadvertent overcorrection. Hypertonic saline should be infused at rates lower than those predicted by formulas with close monitoring of serum sodium and urine output.

Clin J Am Soc Nephrol 2: 1110–1117, 2007. doi: 10.2215/CJN.00910207

Hypertonic saline was first used to treat hyponatremia in 1938 (1), and it is still generally accepted as the treatment of choice for hyponatremic emergencies (2,3). However, in many medical centers, hypertonic saline is rarely used; fear of complications—most notably the osmotic demyelination syndrome (ODS), a neurologic disorder thought to result from rapid correction of hyponatremia (4)—may be responsible for its limited use.

Clinicians have few data to guide them in the optimal use of hypertonic saline. Although guidelines for rates of infusion and monitoring procedures can be found in the literature (2,5),remarkably few studies have reported on dosage–response relationships. Formulas based on the apparent distribution of sodium in total body water (2,6–8) have been widely used clinically to predict the rise in serum sodium in response to hypertonic saline. However, it is not clear how accurately these calculations predict correction rates in clinical use of hypertonic saline: only one of these formulas was recently evaluated prospectively in a small number of patients (9).

We report our experience with hypertonic saline use for the treatment of hyponatremia in 62 patients during a 5-yr period in a 528-bed, acute care, teaching hospital. Previous observational studies reported from our institution have shown that ODS can usually be avoided in severely hyponatremic patients by limiting correction rates to no more than 12 mEq/L in 24 h and 18 mEq/L in 48 h (4,10,11). For many years, as a matter of policy, hypertonic saline use has been overseen by a single group of nephrologists to ensure adherence to these guidelines. This experience provided us with a unique opportunity to assess the pattern of hypertonic saline use and the clinical impact of these guidelines on outcomes and safety. In addition, we assess the accuracy of a commonly used formula in predicting the rise in serum sodium.

Concise Methods

After institutional review board approval, paper charts and electronic health records of all cases of 3% saline use at Rochester General Hospital between December 1999 and December 2004 were reviewed. We excluded patients who were younger than 18 yr or those to whom hypertonic saline was administered for indications other than hyponatremia or was administered by any route other than intravenous.

Received February 21, 2007. Accepted June 21, 2007.

Published online ahead of print. Publication date available at www.cjasn.org.

Correspondence: Dr. Hashim K. Mohmand, 8072 Plantation Drive, West Chester, OH 45069. Phone: 513-280-1191; Fax: 513-558-4399; E-mail: hashimkm@yahoo.com

ISSN: 1555-9041/206–1110

Data collected included demographics, medical history, clinical presentation, physical and laboratory findings, urine output, suspected complications, and volume status as assessed by the treating physician. The volume and duration of hypertonic saline infusion and the clinical setting in which it was started were also noted. Physicians' notes were reviewed for their sense of syndrome of inappropriate antidiuretic hormone secretion (SIADH) as being the cause of hyponatremia. Serum sodium concentrations within 4 h of the 24- and 48-h marks from the time of initiation of infusion were used to calculate the rates of change in serum sodium concentration.

Patients whose serum sodium concentrations, after hypertonic saline infusion, rose >12 mEq/L in 24 h or 18 mEq/L in 48 h were considered as having failed to have met the goals of correction of hyponatremia. The Adrogué-Madias formula, shown as follows, is a widely used tool to predict the change in serum sodium levels in response to intravenous fluids (2,9):

$$\text{Change in serum sodium concentration with 1L of infusate} = \frac{\text{Infusate sodium concentration} - \text{Serum concentration}}{\text{Total body water} + 1}$$

To test the predictive accuracy of this formula, we looked at the patients whose charts contained sufficient data to apply this formula—namely the gender and weight of the patient, the sodium concentrations at the time intervals described previously, and volume of hypertonic saline infused. The formula was then applied, as recommended (2), to predict the change in sodium concentration that would be expected to be caused by the hypertonic saline infusion. This change in sodium level was termed the "expected rise in sodium."

Any change in mental status was considered to be due to hyponatremia when the symptoms were present before and resolved after the correction of hyponatremia. Complications were considered to be due to hypertonic saline therapy when there was any documentation of seizures, pulmonary edema, or neurologic dysfunction during or after the infusion and when no alternative explanations for those complications were found. Charts and available imaging results were reviewed for any clinical or radiologic findings consistent with ODS.

The data were analyzed using Minitab 14 (Minitab Inc., State College, PA). Normally distributed variables are summarized with mean ± SEM, and for non-normal data, medians (interquartile range [IQR]) are used. Statistical significance was assessed for discrete variable by χ^2 analysis or Fisher exact test and for continuous variables by t test or Kruskal-Wallis test, as appropriate. Linear regression was used to look for correlation between continuous variables. This study had no external funding source.

Results

Ninety-two instances of 3% saline use were identified. Thirty patients met the exclusion criteria. The remaining 62 patients were included in the analysis. In 45 patients, the documentation contained sufficient information to apply the Adrogué-Madias formula to calculate the effect of hypertonic saline infusion on serum sodium concentration.

Demographics

Our study population was predominantly white (92%) and female (74.2%). Median age was 76.5 yr (IQR 62.8 to 84.0 yr). The women, as in the previously published series from our institution (10), tended to be older (median age 77.5 yr; IQR 67.5 to 85.0 yr) than men (median age 69 yr; IQR 56.2 to 80.7 yr; $P = 0.075$ by Kruskal-Wallis test). The most commonly encountered (see Table 1) associated conditions were hypertension (71%), psychiatric disorders (32.3%), congestive heart failure (24.2%), diabetes (21%), and malignancy (19.3%). Eighteen (29%) patients were taking a thiazide diuretic, 10 (16.1%) a loop diuretic, and 15 (24.2%) selective serotonin reuptake inhibitors (SSRI).

Clinical Findings

With the use of previously reported definitions (10,11), hyponatremia was chronic in 47 (76%) and acute (hospital acquired or associated with psychogenic polydipsia) in 15 (24%) patients. Six (10%) patients had seizures at presentation, none of which was ongoing at the time of hypertonic saline administration. Of these, five patients had preexisting seizure disorder. Nine (15%)

Table 1. Baseline clinical characteristics

Characteristic	*n*	%
Gender		
male	16	25.8
female	46	74.2
Ethnicity		
white	57	92
black	1	1.6
Hispanic	2	3.2
other	2	3.2
Associated conditions		
history of heart failure	15	24.2
chronic liver disease	4	6.5
chronic renal insufficiency	3	4.8
acute renal failure	10	16.1
hypothyroidism	11	17.7
recent surgery (within past 7 d)	5	8.1
chronic obstructive pulmonary disease	8	12.9
clinical impression of SIADH	39	62.9
psychiatric disorders	20	32.3
polydipsia	8	12.9
coronary artery disease	12	19.3
diabetes	13	21.0
hypertension	44	71.0
alcoholism	6	9.7
malignancy	12	19.3
history of seizures	12	19.3
Medications		
thiazide diuretics	18	29.0
loop diuretics	10	16.1
Selective serotonin reuptake inhibitors	15	24.2

patients were unresponsive, somnolent, or obtunded. The remaining patients had a variety of nonspecific complaints, including confusion, disorientation, lethargy, nausea, vomiting, dizziness, weakness, gait disturbances, and falls (two with fractures). Three patients had neurosurgical conditions (subdural hematoma and pituitary surgery) that, in addition to their symptoms, prompted hypertonic saline. The mean sodium concentration at presentation was 116.9 ± 0.9 mEq/L. Mean urine osmolality was 431 ± 22 mOsm/kg. Forty-six (74.2%) patients were euvolemic, and of these, 39 (62.9%) were considered to have SIADH by the treating physicians. One (1.6%) patient each was hypervolemic and hypovolemic; the remaining 14 (22.6%) patients had an indeterminate volume status and multiple coexisting risk factors for hyponatremia.

Clinical Setting

Hypertonic saline infusion was started in the emergency department (ED) in 19 (30.7%) patients, in the intensive care unit (ICU) in 9 (14.5%) patients, and on medical floors in 34 (54.8%) patients. In 84% of all patients and in 100% of patients with serum sodium <120 mEq/L, a nephrologist supervised the administration of hypertonic saline.

Because of either the absence of serious neurologic symptoms or unsuccessful attempts to increase the serum sodium concentration without hypertonic saline, there were substantial delays between the diagnosis of hyponatremia and the initiation of hypertonic saline therapy. In the ED, the median delay in the initiation of hypertonic saline therapy from the time of presentation was 5.6 h (IQR 4.3 to 8.0 h). This delay was significantly short when compared with the median delay of 16.5 h (IQR 12.0 to 27.6 h) on the medical floors ($n = 43$; $P < 0.001$) and with the ICU ($n = 26$; $P = 0.005$), where the median delay was 13.2 h (IQR 8.0 to 27.0 h). The delay in initiating therapy was significantly short ($n = 52$; $P = 0.04$ by Kruskal-Wallis test) when the sodium level at presentation was <110 mEq/L (7.3 h; IQR 4.0 to 10.0 h) than when it was ≥110 mEq/L (14.0 h; IQR 6.3 to 21.0 h). The physicians responded by ordering hypertonic saline approximately twice as quickly when the patients were either obtunded or having seizures (median response time 4 h; IQR 2 to 10 h) than when they were not (median 8.8 h; IQR 4.0 to 16.5 h), but this did not reach statistical significance ($n = 58$; $P = 0.16$ by Kruskal-Wallis test).

Response to Treatment

The median rate of administration of hypertonic saline was 23.5 ml/h (IQR 17.0 to 32.2 ml/h). In the 45 patients whose body weight was recorded, the median rates of infusion were 0.38 ml/kg per h (IQR 0.25 to 0.50 ml/kg per h) or 0.19 mmol/kg per h (IQR 0.13 to 0.25 mmol/kg per h). The median amount of hypertonic saline infused was 386.5 ml (IQR 241.0 to 707.0 ml). The mean serum sodium concentration before the administration of hypertonic saline was 117.5 ± 0.8 mEq/L (Figure 1).

During the infusion of hypertonic saline, the increase in serum sodium level averaged 7.5 ± 0.7 mEq/L and the average rate of rise in sodium concentration was 0.47 ± 0.05 mEq/L per h. The average change in serum sodium concentration during the first 24 h after hypertonic saline therapy was 7.1 ± 0.6 mEq/L and during the first 48 h was 11.3 ± 0.7 mEq/L. As might be expected, the increase in sodium concentration was significantly related (Figure 2) to pretreatment sodium concentration ($R^2 = 0.43$; $P < 0.001$). There were no significant differences in the rates of rise in sodium concentration among the clinical settings.

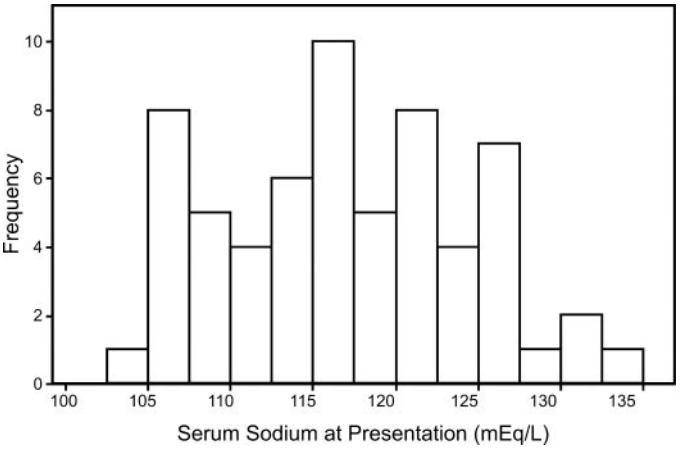

Figure 1. Distribution of serum sodium at presentation.

In seven (11.3%) of 62 patients, the increase in serum sodium concentration during the first 24 h exceeded 12 mEq/L and, in six (9.7%) patients, the increase in the first 48 h exceeded 18 mEq/L. The 10 (16.1%) patients whose correction rates exceeded either of these two limits (in three patients, the correction rate exceeded both limits) were designated "overcorrectors." The mean pretreatment sodium concentration in overcorrectors was 111.9 ± 1.5 mEq/L, significantly lower than the pretreatment sodium concentration in patients whose correction rates remained within guidelines (mean 118.5 ± 0.8; $P = 0.002$ by t test; $n = 62$). Fifteen (28.9%) of the 52 nonovercorrectors missed overcorrection marks by 1 or 2 mEq/L; these were designated as "near misses." Furthermore, all of the overcorrectors had pretreatment serum sodium concentrations <120 mEq/L. Therefore, we conducted a subgroup analysis in

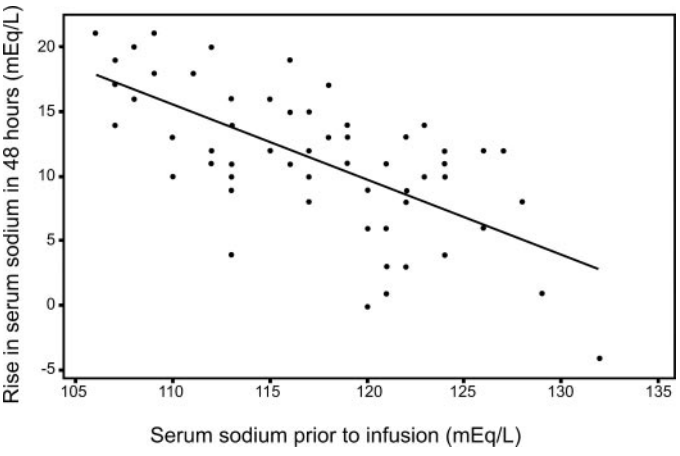

Figure 2. Relationship of rise in sodium at 48 h to preinfusion sodium concentration.

Table 2. Clinical features of the overcorrectors[a]

Patient	Gender	Age (yr)	Volume Status	Thiazide Diuretic	Urine Osmolality (mOsm/L)	Volume of Hypertonic Saline (ml)	Sodium before Infusion (mEq/L)	Rise in Serum Sodium (mEq/L) at		Water Diuresis?	Dextrose Water Used?
								24 h	48 h		
3	F	69	Euvolemic	Yes	228	N/D	106	16	21	Yes	Yes
15	F	81	Indeterminate	Yes	429	292	115	14	16	N/D	N/D
19	F	84	Euvolemic	No	480	744	118	15	17	N/D	N/D
29	F	57	Indeterminate	No	271	195	109	11	21	N/D	Yes
37	F	63	Euvolemic	No	425	48	112	16	20	Yes	N/D
43	M	53	Hypovolemic	Yes	–	60	108	12	20	Yes	N/D
49	F	87	Euvolemic	Yes	90	N/D	109	16	18	Yes	Yes
51	F	91	Euvolemic	Yes	472	460	107	13	19	N/D	N/D
56	F	58	Indeterminate	Yes	272	376	116	10	19	N/D	N/D
57	F	75	Euvolemic	No	–	540	119	13	14	N/D	N/D

[a]N/D, not documented.

the 37 patients whose serum sodium concentration was <120 mEq/L to define the factors that were associated with excessive rise in sodium concentration.

Among patients with a pretreatment serum sodium concentration <120 mEq/L, the increase in serum sodium level during the infusion of hypertonic saline averaged 8.7 ± 0.8 mEq/L, and the average rate of correction of hyponatremia was 0.5 ± 0.1 mEq/L per h. The average change in serum sodium concentration during the first 24 h after hypertonic saline therapy was 8.5 ± 0.7 mEq/L and during the first 48 h was 14 ± 0.6 mEq/L. Overcorrectors received significantly *less* hypertonic saline (median 334 ml; IQR 94 to 520 ml) than patients whose correction rates remained within guidelines (median 640 ml; IQR 305 to 932 ml; $P = 0.04$; $n = 31$); however, the rate of hypertonic saline infusion was significantly higher in the overcorrected group (median 0.49 [IQR 0.44 to 0.59] *versus* 0.29 [IQR 0.25 to 0.42] ml/kg per h; $P = 0.038$; $n = 31$). Furthermore, the overcorrectors had significantly more serum sodium values obtained in the first 24 h (median 6.0; IQR 5.0 to 6.2) than patients who were not overcorrected (median 4; IQR 4 to 5; $P = 0.01$; $n = 37$). Four of the 10 overcorrectors had water diuresis that emerged during the course of therapy, documented by low urine osmolality or high urine output (Table 2). In three of the overcorrectors, there was documented use of 5% dextrose water in an effort to blunt the rapid increase in serum sodium concentration. In one patient, 5% dextrose water and DDAVP were administered after an increase in serum sodium concentration of 16 mEq/L in 18 h; with this intervention, the serum sodium concentration was successfully lowered and the patient remained within the 24- and 48-h goal limits.

Eleven (29.7%) patients received concurrent potassium chloride infusion (mean 55.5 mmol). Concurrent administration of potassium chloride was more prevalent in the overcorrected group, but the difference did not reach statistical significance ($P = 0.09$ by Fisher exact test). The mean pretreatment serum potassium concentration was 3.7 mEq/L ± 0.1, and only one patient had serum potassium concentration <2.5 mEq/L.

Predictive Accuracy of Adrogué-Madias Formula

The increase in serum sodium concentration that could be expected from the hypertonic saline infusion was calculated in 45 patients (31 of these had pretreatment sodium concentrations <120 mEq/L) using the formula proposed by Adrogué and Madias (2,9) and is referred to as the "expected increase" in serum sodium concentration. The ratio of the actual increase in serum sodium concentration to the expected increase in serum sodium concentration during therapy is shown in Figure 3. A value of 1 in this ratio indicates that the entire increase in serum sodium concentration can be accounted for by the administered hypertonic saline; a value <1 indicates that the actual increase is less than would be predicted; and a value >1 indicates that the actual increase in serum sodium concentration exceeds the predicted increase. As shown in Figure 3, in patients with serum sodium concentrations <120 mEq/L, the actual increase in serum sodium

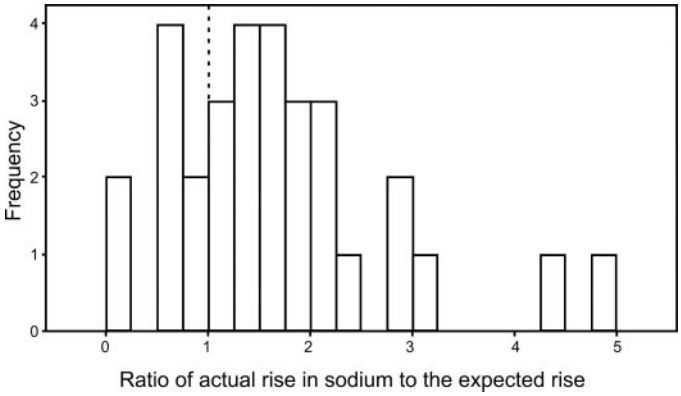

Figure 3. Ratio of actual to expected rise in sodium as calculated using the Adrogué-Madias formula. A value of 1 indicates that the entire increase in serum sodium concentration can be accounted for by the administered hypertonic saline. In 74.2% of the patients with preinfusion sodium <120 mEq/L, the ratio was >1, indicating that the actual increase exceeded the predicted increase. The formula also underestimated the increase in sodium concentration for the study population as a whole.

concentration exceeded the expected increase in 74.2% of the patients, and the average ratio of actual to expected was 1.66 ± 0.2. In overcorrectors, the ratio was significantly higher than in patients who were not overcorrected (2.4 [IQR 1.6 to 2.9] *versus* 1.3 [IQR 0.7 to 1.9]; $P = 0.006$ by Kruskal-Wallis test; $n = 31$). Among patients with a pretreatment serum sodium concentration <120 mEq/L, there were no significant differences between the overcorrectors and the nonovercorrectors in use of medications or comorbidities, with the exception of psychiatric disorders, which were more prevalent among the overcorrectors ($P = 0.049$ by Fisher exact test).

Complications of Hypertonic Saline Use

There were no documented cases of ODS. Ten (16.1%) patients had preexisting neurologic dysfunction that persisted after hypertonic saline infusion. Each of these had an alternative cause

Table 3. Neurologic outcomes in patients who were treated with hypertonic saline solution[a]

Patient	Age	Gender	Outcome	Volume of 3% Saline (ml)	Plasma Sodium Concentration (mEq/L)			Suspected Cause of Neurologic Dysfunction
					Pretreatment	At 24 h	At 48 h	
1	62	F	N, S	200	122	125	130	History of seizure disorder and previously documented change in mental status with increased dosage of antiseizure medication
10	81	F	N	500	116	125	127	Confusion and severe dementia at baseline that remained unchanged
25	46	F	S	N/D	128	126	136	Known history of seizure disorder; had repeated seizures before, during, and after the correction of hyponatremia; normal mental status between seizures
30	77	F	N, S	995	124	135	135	Advanced nasopharyngeal cancer with preexisting metastatic intracranial lesions
38	78	M	N	140	122	127	131	Longstanding confusion from past strokes and ongoing severe sepsis
39	86	F	N	695	118	125	131	Preexisting mental status changes as a result of severe sepsis, and hypoxemia from pneumonia
42	72	M	N	280	110	121	123	Brain metastases from primary lung cancer
50	37	M	N	789	119	126	130	Subarachnoid hemorrhage
58	71	F	N	525	120	120	120	Progressive, terminal azotemia from bilateral hydronephrosis secondary to end-stage uterine cancer
59	55	F	N	N/D	124	129	134	Admitted with pulmonary embolism, persistent hypoxia and hypotension, invasive chronic lymphocytic leukemia, and multiorgan system failure; persistent, preexisting confusion of unclear cause that did not change with correction of plasma sodium concentration; discharged to hospice care

[a]N, persistent neurologic dysfunction (before, during, or after hypertonic saline infusion); S, seizure.

for persistent neurologic dysfunction (Table 3), and none of these patients was overcorrected. There were no respiratory arrests before or during hypertonic saline infusion despite slow rates of rise in sodium concentration and long delays in starting the infusions. One patient, patient 58, also developed fluid overload because of progressive renal failure. Two patients died during the same admission from causes unrelated to hypertonic saline therapy (cardiac arrest and progressive azotemia from bilateral hydronephrosis).

Discussion

Some authorities have suggested that hypertonic saline should be used only in critical care units (12) or that it be limited to patients with repeated convulsions, agitated confusion, or coma (13). At our institution, hypertonic saline is permitted outside the critical care units, but oversight by nephrologists is strongly encouraged and is required for administration of >200 ml. Although hypertonic saline is accepted as a treatment for hyponatremic seizures, this was rarely the indication. Rather, hypertonic saline was used when it was believed that isotonic saline or water restriction alone was unlikely to increase the serum sodium concentration promptly. In most patients, the rate of infusion was modest, the median being 0.38 ml/kg per h—a rate that would be expected to increase the serum sodium concentration by <0.5 mEq/L per h (2). Hypertonic saline was administered in three different clinical settings: ED, ICU, and medical wards. Although there were significant differences in the time taken by the physicians to respond to low sodium levels—likely a result of the inherent differences between these settings with regard to the rapidity of phlebotomy, laboratory processing times, and medication dispensing as well as nurse staffing—the clinical setting did not seem to have an impact on either the rates of overcorrection or the neurologic outcomes.

We were successful in maintaining a rate of rise in sodium concentration ≤12 mEq/L per d and 18 mEq/L in 48 h in 84% of patients, and in all patients correction remained well below 25 mEq/L in 48 h, a rate that is associated with a high incidence of severe posttherapeutic neurologic complications (14). Fortunately, there were no complications in patients who were overcorrected. The favorable outcome depended on frequent interventions by medical housestaff guided by nephrology consultants to modify the rate of infusion of hypertonic saline and in some cases to administer 5% dextrose water and/or DDAVP (in the same dosages used to treat central diabetes insipidus) as "antidote."

Patients who were overcorrected actually received *less* hypertonic saline than those who remained within therapeutic guidelines. This seeming paradox is explained by the downward adjustments in the rate of infusion that occurred in response to more rapid increases in the serum sodium concentration. Indeed, in some patients, not only was hypertonic saline stopped, but also therapeutic rescue with 5% dextrose water and/or DDAVP was required because of the unanticipated emergence of a water diuresis during therapy.

Predictive equations are based on the relationship among the serum sodium concentration, total body exchangeable sodium and potassium, and total body water as defined empirically by Edelman *et al.* (6). Although clinically popular formulas are reasonably accurate in predicting the increase in serum sodium concentration from hypertonic saline infusion, in our experience, the formula tended to underestimate the increase, and in overcorrectors, the actual increase in sodium concentration was up to five times the predicted rate. The predictive formula that we used omits both potassium and the intercept in Edelman's empirical relationship (6,15,16). Severe hypokalemia was infrequent and potassium replacement was modest in this series.

Liamis *et al.* (9) recently prospectively evaluated the Adrogué-Madias formula in patients with dysnatremias, including hypertonic saline with intravenous furosemide, in 10 patients with SIADH. The degree of hyponatremia, however, was much less severe (average pretreatment sodium was 122.6 ± 5 mEq/L, compared with 117.4 ± 0.8 mEq/L in our series and 111.9 ± 1.5 mEq/L in the overcorrectors). In addition, the investigators' concurrent use of furosemide may have helped prevent spontaneous water diuresis that frequently accompanied overcorrection in our series. In patients with SIADH, the difference between the actual and predicted serum sodium after 12 h of 3% saline did not reach statistical significance; nevertheless, the actual increase was 1.5 mmol/L higher than the 4.8 mmol/L increase predicted—a 31% discrepancy. The discrepancy was of similar magnitude in patients with thiazide-induced hyponatremia and was much greater in patients with polydipsia. These discrepancies, because of the small number of patients, did not reach statistical significance, but these data, although limited, highlight the limitation of the Adrogué-Madias formula in predicting change in sodium concentration with hypertonic saline therapy.

Although many of the overcorrectors in our series were perceived to be euvolemic and as having definite SIADH by the attending nephrologists, their response to hypertonic saline infusion is suggestive of multifactorial causes for the hyponatremia, possibly including undiagnosed hypovolemia and other reversible impairments of water excretion. Indeed, as is seen in practice, an accurate clinical assessment of volume status is often extremely difficult (17), especially in elderly patients with altered mental status. In such cases, the rapid volume expansion from hypertonic saline infusion can *appropriately* suppress ADH secretion, effect a water diuresis, and result in a rapid rise in serum sodium concentration. Although establishing volume status remains an important part of the traditional diagnostic approach to hyponatremia, when approaching a patient from the therapeutic standpoint, the clinician needs to be cognizant that establishing volume status accurately may not be possible. One such case is presented next to illustrate this point.

An 87-yr-old woman who was treated long term with hydrochlorothiazide for hypertension was admitted with a serum sodium of 106 mEq/L and a serum potassium of 2.6 mEq/L 2 wk after starting treatment with an SSRI. The thiazide and the antidepressant were stopped, and she was given isotonic saline and potassium replacement; however, her serum sodium increased only by 3 mEq/L during her first 14 h in the hospital, and her urine output was 60 ml/h. Therefore 3% saline was

prescribed at 20 ml/h. A few hours later, diuresis developed with a recorded urine output of 1950 ml in 7 h and urine osmolality of 90 mOsm/kg. Hypertonic saline was discontinued when the serum sodium was 118 mEq/L, after 120 ml had been administered (enough to increase the serum sodium by a calculated 3 mEq/L). However, primarily because of the water diuresis, the serum sodium increased from 109 to 124 mEq/L in 18 h. Therefore, 5% dextrose in water was prescribed, successfully preventing any further increase in sodium concentration. This case illustrates several of the problems that we have encountered at our hospital while treating patients for hyponatremia with hypertonic saline:

1. There is often ambiguity as to the cause of hyponatremia; was this patient's hyponatremia the result of thiazide diuretic and volume depletion, or was it due to SIADH caused by an SSRI?
2. The patient's condition often changes over time; initially this patient failed to respond to isotonic saline, suggesting that her hyponatremia was due to SIADH, but then a water diuresis emerged, reflecting discontinuation of the diuretic or the SSRI or a response to volume repletion.
3. Attempts to predict the increase in serum sodium to be expected from 3% saline are often inaccurate; in this case, the calculated increase was one fifth the increase that actually occurred.

Some authors have drawn a distinction between "symptomatic" and "asymptomatic" hyponatremia, arguing that patients with symptoms should be treated with hypertonic saline by at least 1 to 2 ml/kg per h (12). Our experience suggests that for most patients with symptomatic hyponatremia, this aggressive approach may not be necessary, and we are unaware of any data showing that it produces better results than the more conservative approach that we have used. As others have reported (18,19), most patients with hyponatremia have at least subtle symptoms, and in our patients, these symptoms did not worsen or lead to respiratory arrests during treatment despite rates of correction that are considerably slower than what others have reported. We do not dispute the recommendation that patients with active seizures or impending herniation be given 100-ml bolus infusions of hypertonic saline (12); however, we did not encounter any patients with such a presentation in this series. Similarly, case series (14,20) reporting a favorable outcome with more aggressive therapy did not include such patients.

In our series, although the overcorrectors received less hypertonic saline, they also received it at a more rapid rate than patients whose correction rates remained within guidelines. Moreover, the infusion rate in both of these groups was well below the 1- to 2-ml/kg per h rate as has been recommended. On the basis of this experience, especially when uncertainty regarding the volume status exists, it may be desirable to initiate hypertonic saline therapy with even slower rates than those formerly recommended and those predicted by the popular formulas, particularly in chronically hyponatremic patients with modest symptoms.

Even with careful oversight by medical residents and nephrology consultants and despite rates of infusion that are considerably slower than what others have used, the number of "near misses" in our series was disturbingly high. Regardless of how much hypertonic saline is used or how fast it is infused, clinicians should recognize that the increase in serum sodium concentration cannot be reliably predicted by formulas and that frequent monitoring of the urine output and serum sodium concentrations is mandatory.

Acknowledgments

Some of these data were presented as an abstract at the annual meeting of the American Society of Nephrology; November 14 through 19, 2006; San Diego, CA.

Disclosures

None.

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See related editorial, "The Adrogue-Madias Formula Revisited," on pages 1098–1099.

Nephrol Dial Transplant (2008) 23: 3501–3508
doi: 10.1093/ndt/gfn476
Advance Access publication 22 August 2008

Original Article

NDT
Nephrology Dialysis Transplantation

Can we really predict the change in serum sodium levels? An analysis of currently proposed formulae in hypernatraemic patients

Gregor Lindner[1,2,*], Christoph Schwarz[3,*], Nikolaus Kneidinger[1], Ludwig Kramer[1], Rainer Oberbauer[2,3] and Wilfred Druml[2]

[1]Intensive Care Unit 13H1, Clinic for Internal Medicine III, [2]Department of Nephrology and Dialysis, for Internal Medicine III, Medical University of Vienna, Vienna and [3]Department of Nephrology, Krankenhaus der Elisabethinen, Linz, Austria

Abstract

Background. Hypernatraemia is common in intensive care patients and may present an independent risk factor of mortality. Several formulae have been proposed to guide infusion therapy for correction of serum sodium. Unfortunately, these formulae have never been validated comparatively. We assessed the predictive potential of four different formulae (Adrogué–Madias, Barsoum–Levine, Kurtz–Nguyen and a simple formula based on electrolyte-free water clearance) in correction and maintenance of serum sodium in 66 hyper- and normonatraemic ICU patients.

Methods. With daily measurements of sodium/potassium and fluid/electrolyte balances, a day-to-day prediction of serum sodium levels was calculated using the four formulae. This was compared to the measured changes in serum sodium.

Results. Six hundred and eighty-one patient-days (194 hypernatraemic) in 66 patients were available for calculations. Prediction of serum sodium levels using all four formulae correlated significantly ($P < 0.05$) with measured changes in serum sodium. Individual variations were extreme, and the mean differences (±SD) for predicted versus measured serum sodium were within the range of 3.4–4.5 (±4.4–4.7) mmol/l similar for the Adrogué–Madias, Barsoum–Levine and Nguyen–Kurtz formulae. In comparison, our proposed formula underestimated the changes of serum sodium (mean ± SD −1.5 ± 5.3). During hypernatraemia, the differences between predicted and measured values were even greater (mean ± SD 5.0–6.7 ± 3.9–4.3) using the published formulae compared to our formula (mean ± SD 0.2 ± 4.0).

Conclusions. Currently available formulae to guide infusion therapy in hyper- and normonatraemic states do not accurately predict changes of serum sodium in the individual ICU patient. In clinical practice, infusion therapy should be based on the reasons for hypernatraemia and serial measurements of serum sodium to avoid evolution of derangements.

Keywords: correction; formula; hypernatraemia; prediction; sodium

Introduction

Hypernatraemia is a frequent and clinically relevant electrolyte derangement in the critically ill patients. Its prevalence has been reported to be 5–7% at intensive care units (ICUs) [1,2]. Most cases of hypernatraemia actually develop during a hospital stay, and thus its occurrence has been regarded as an indicator of quality of care [3]. Even small changes in serum sodium are associated with untoward effects, and hypernatraemia has been shown to present an independent risk factor of mortality [1]. The adverse effects of hypernatraemia may be mediated not only by the electrolyte derangement *per se* but potentially also by an inappropriate correction [4–6].

Because of the detrimental effects of hypernatraemia on the course of disease and the outcome, it is of utmost importance for the physician at the ICU to avoid its development. If hypernatraemia is already present, then its appropriate treatment without inducement of therapy-related side effects is the goal. Several formulae have been proposed to serve as a guide for infusion therapy of dysnatraemic states [7–9]. These mathematical approaches simplify the mechanisms of sodium and water handling and have major limitations [10]. Unfortunately, only one of these formulae was assessed in a larger clinical study regarding the potential in predicting serum sodium concentrations [11]. Some formulae actually were only evaluated in hypothetical cases [8,9].

These formulae were primarily created for the guidance of correction of hyper- and hyponatraemia. With the aim of avoiding the evolution of dysnatraemic states, it is of further interest whether such formulae are also capable to predict the day-per-day change of serum sodium levels in

Correspondence and offprint requests to: Gregor Lindner, Department of Nephrology and Dialysis, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Wien, Austria. Tel: +43-650-412-74-22; Fax: +43-1-40400-4386; E-mail: lindner.gregor@gmail.com
*Both authors contributed equally to this study.

normonatraemic patients in order to preserve the electrolyte balance.

In this retrospective study, we assessed in ICU patients, in whom complete information on electrolyte and water balance was available, the predictive value of three formulae generally proposed for the guidance of infusion therapy. Additionally, a formula incorporating electrolyte-free water loss was assessed. These different formulae were evaluated both in patients with hypernatraemia with the aim of correcting it, and in patients with normonatraemia of maintaining electrolyte equilibrium.

Subjects and methods

A retrospective analysis was performed in 66 intensive care patients with at least one episode of hypernatraemia during the stay on the ICU. All patients with hypernatraemia at the time of admission to the ICU were excluded from the study. A day-per-day prediction of serum sodium levels was obtained based on the currently available formulae (see the Appendix) for the prediction of the change in serum sodium levels in hypernatraemic as well as normonatraemic patients.

We used the Adrogué–Madias, the Barsoum–Levine and the Kurtz–Nguyen formulae and a formula based on the calculation of the electrolyte-free water clearance (EFWC) proposed by ourselves [7–9]. Because not all of the formulae were designed for the prediction of the day-to-day serum sodium concentration, some mathematical derivations had to be made (see the Appendix). At least the calculations were done using the following formulae (for abbreviations see the Appendix).

Adrogué–Madias formula:

$$Na_2 = \frac{(Na_1 \times TBW) + [Vol_{inf} \times (Na + K)_{inf}]}{TBW + Vol_{inf}}, \quad (1)$$

Barsoum–Levine formula:

$$Na_2 = \frac{(TBW \times Na_1) + [Vol_{input} \times (Na + K)_{input} - Vol_{out} \times (Na + K)_{out}]}{TBW + \Delta Vol}, \quad (2)$$

EFWC formula:

$$Na_2 = \frac{Na_1 \times TBW}{TBW - EFWC}, \quad (3)$$

Kurtz–Nguyen formula:

$$Na_2 = \frac{[(Na_1 + 23.8) \times TBW] + [1.03 \times [(Na + K)_{input} - (Na + K)_{out}]]}{TBW + \Delta Vol} - 23.8. \quad (4)$$

According to the adapted formula, the next day serum sodium concentration was calculated by the pre-day serum sodium level and total body water (TBW) together with the inputs and the outputs of fluid volume, sodium and potassium within 24 h. The predicted and measured sodium levels were compared statistically.

The 66 patients stayed for a total of 1034 days at the ICU. In the end, 681 days of intensive care stay were able to be used in the analysis. The day of admission (66 days) could not be included in the analysis as well as an additional 277 days because of the lack of data for the calculation of the formulae. Furthermore, 10 observation days were excluded from the analysis because of severe diarrhoea.

The following daily measured parameters were recorded for the analysis:

Serum: sodium, potassium, osmolality.

Total daily outputs and inputs of volume and sodium–potassium concentration.

Outputs

(1) Urine: daily volume, sodium, potassium and osmolality.
(2) Drainage tubes: nasogastric suction, wound drains, pleural effusion; volume, sodium and potassium concentration based on empirical data. The fluid of nasogastric suction was calculated with a sodium/potassium concentration of 110 mmol/l. Pleural effusion and wound drains were calculated as isotonic fluids.

Inputs

The volume and the sodium and potassium concentration of

(1) intravenous fluid including volume replacement,
(2) solvent solutions for medications (sodium content of antibiotics was not included) and
(3) enteral and parenteral nutrition solutions.

To ensure practicability in the daily routine, some assumptions had to be made, which potentially may affect the results of the calculations. At normal body temperature, oxidation water formation equals perspiration and therefore no volume change will occur during normal body temperature and adequate nutrition [12]. Any increase in body temperature will lead to an augmentation in perspiration. In the case of fever, perspiration could only be calculated from the standard formula but not measured.

Because body temperature often changes (due to fever lowering medication) over 24 h, it is not possible to calculate perspiration per day individually. Therefore, perspiration was not included in the current ongoing losses in all formulae. Moreover, the measurement or calculation of gastrointestinal losses (volume and electrolytes) via stool is

not possible to measure in the daily routine. So stool losses were not included in the calculations, and patient-days with documented severe diarrhoea were eliminated from the study ($n = 10$).

TBW was calculated as body weight × 0.6 for men and body weight × 0.5 for women [12]. Because it is rather difficult to weigh the patients daily on the ICU, daily TBW calculation was done according to the fluid balances (total volume input − total loss volume).

Statistics

The purpose of the study was to analyse the predictive value of four different formulae on longitudinal serum sodium levels in ICU patients with hyper- and normonatraemia. A linear regression analysis was performed to estimate r^2 for analysing how much of the variability of the predicted values may be explained by the variability of measured values. The variability of predicted values along the measured range of serum sodium levels is provided as the Bland–Altman plot [13]. Residual statistics of the linear models are provided in a separate supplemental data sheet.

This study was approved by the Ethics Commission of the Medical University of Vienna, Austria.

Results

The demographics of the included patients are given in Table 1. All patients developed hypernatraemia at least once during the ICU stay. The all-cause mortality was 42%. Causes of ICU-acquired hypernatraemia were defined as follows: positive sodium balance, administration of loop diuretics, osmotic diuresis, renal failure, extrarenal water losses and diabetes insipidus (multiple choices were possible). The most common mechanism for the development of ICU-acquired hypernatraemia was an increase in free water loss due to the disturbance of the renal concentration mechanism. Renal concentration defects were defined as a urine osmolality of <800 mmol/l during the rise of serum sodium. The increase in renal free water loss includes administration of furosemide (35%), osmotic diuresis (35%) and renal failure (20%). An exaggerated sodium intake due to the administration of sodium-rich infusions and/or nutritions accounted for 48% of cases of ICU-acquired hypernatraemia and thus was the most important single mechanism for the development of hypernatraemia. Extrarenal water losses due to fever (8%) or via tubes (7%) were rare causes for the loss of free water.

A single mechanism for hypernatraemia was identified in 50 periods. Two simultaneous mechanisms for hypernatraemia were identified in 20 periods and three mechanisms in 6 periods. Mean central venous pressure was 14.1 (±6.0) indicating that most patients were at least eu- or hypervolaemic during hypernatraemia. The average duration of hypernatraemia was 2 days in our patients. Almost all patients (>90%) developed hypernatraemia during their first 7 days of ICU stay. The mean individual daily changes in serum sodium were ∼1.5 ± 3.5 mmol/l.

According to the serum sodium level on Day 1, we measured ongoing sodium, potassium and water inputs and outputs (for 24 h) and calculated the predicted serum sodium level on Day 2 using different formulae. The calculations were correlated to the real change in the serum sodium level.

We analysed a total of 681 patient-days in 66 patients. The mean ± SD differences for real sodium levels were 4.56 ± 4.36 for the Adrogué–Madias formula, 3.37 ± 4.41 for the Barsoum–Levine formula, −1.47 ± 5.26 for the new EFWC-based formula and 3.93 ± 4.76 for the Kurtz–Nguyen formula. In hypernatraemic stages (194 patient-days) differences in mean ± SD were even greater: 6.68 ± 4.27 for the Adrogué–Madias formula, 4.98 ± 3.91 for the Barsoum–Levine formula and 5.31 ± 4.3 for the Kurtz–Nguyen formula, whereas the difference was 0.16 ± 3.99 and even smaller for the EFWC formula.

As shown in Table 2, all calculations in the total patient group correlated significantly with the serum sodium level on the next day (r^2 0.45–0.51; $P < 0.005$). In the linear regression analysis of hypernatraemic days the correlations were less good, but still significant (r^2 0.1–0.25; $P < 0.005$). Inclusion of perspiration did not further improve correlation coefficients (data not shown).

The data are presented graphically using a Bland–Altman plot (Figure 1). Whereas Adrogué–Madias, Barsoum–Levine and Kurtz–Nguyen overestimated, our own EFWC-based formula slightly underestimated the mean change in serum sodium levels.

Table 1. Patient characteristics and data on outcome

Sex	44 (67%) Male 22 (33%) Female	
Age	59	SD 15
Height (in cm)	171	SD 10.3
Weight (in kg)	83	SD 20.5
BMI	28	SD 5.7
Length of ICU stay	16	SD 12
ICU mortality	42%	
SAPS II score	54	SD 14.6
APACHE III score	63	SD 26.4
Admission	*Percent*	*Number*
Respiratory	35%	23
Neurologic	8%	5
Gastroenterologic + hepatologic	15%	10
Cardiologic	38%	25
Nephrologic	4%	3

BMI, body mass index; ICU, intensive care unit.

Table 2. Correlation of formula prediction and real serum sodium

Formula	All days = 681		Na ≥ 150 days = 191	
Adrogué	$\beta = 0.664$	$r^2 = 0.446$	$\beta = 0.207$	$r^2 = 0.106$
Barsoum	$\beta = 0.684$	$r^2 = 0.516$	$\beta = 0.287$	$r^2 = 0.204$
EFWC	$\beta = 0.551$	$r^2 = 0.453$	$\beta = 0.297$	$r^2 = 0.248$
Kurtz	$\beta = 0.623$	$r^2 = 0.483$	$\beta = 0.243$	$r^2 = 0.170$

Adrogué: Adrogué–Madias formula; Barsoum: Barsoum–Levine formula; EFWC: electrolyte-free water clearance formula; Kurtz: Kurtz–Nguyen formula; β: slope; r^2: *r*-squared.
All $P < 0.005$.

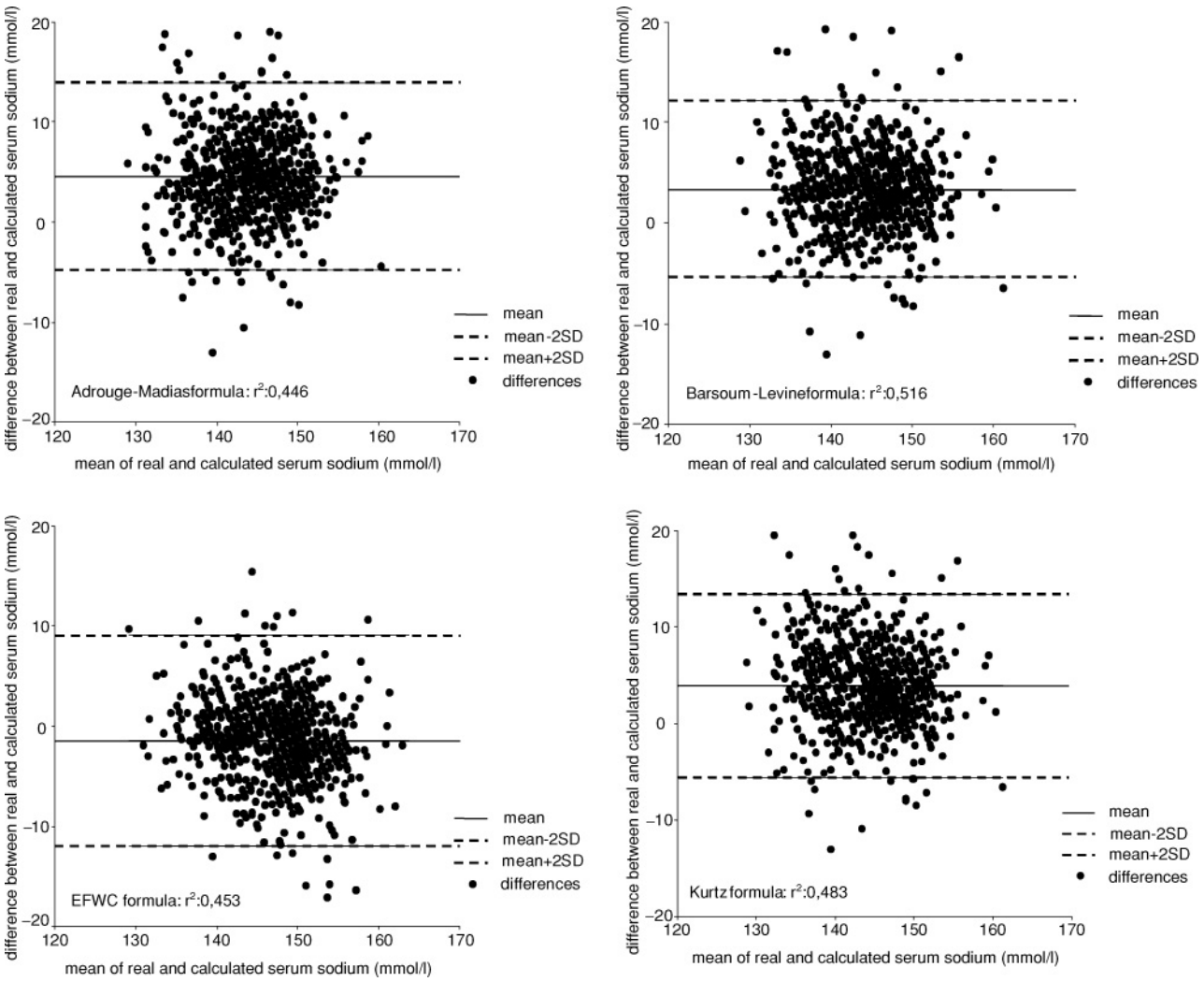

Fig. 1. Bland–Altman plot of all formulae compared to real sodium levels.

Table 3. Results of linear regression analysis using three groups according to rise or fall in serum sodium

Formula	Rise >3 mmol/l	Decline >3 mmol/l	Rise/fall <3 mmol/l
Adrogué	$r^2 = 0.5$	$r^2 = 0.4$	$r^2 = 0.52$
Barsoum	$r^2 = 0.5$	$r^2 = 0.41$	$r^2 = 0.57$
Kurtz	$r^2 = 0.47$	$r^2 = 0.39$	$r^2 = 0.54$
EFWC	$r^2 = 0.43$	$r^2 = 0.51$	$r^2 = 0.7$

Adrogué: Adrogué–Madias formula; Barsoum: Barsoum–Levine formula; EFWC: electrolyte-free water clearance formula; Kurtz: Kurtz–Nguyen formula; r^2: *r*-squared.

Whereas for the whole group there was a rather good correlation between measured and predicted serum sodium concentrations, there were large variations in individual patients (Figure 1), the highest accounting for 10–15 mmol/l with all tested formulae. The predictions of daily serum sodium changes were not statistically different with all used formulae if the serum sodium level either increased/decreased by >3 mmol/l/day or was stable (Table 3).

Discussion

In this investigation, we have conducted for the first time in a systematic manner a comparison of four formulae advocated for guidance of infusion therapy in hyper- and normonatraemic states in the ICU setting. We have shown that in the overall group, there was a good correlation between the predicted and observed changes in serum sodium concentration, but the formulae were absolutely inadequate in predicting serum sodium in the individual patient. A formula taking into account the electrolyte-free water loss allowed the most accurate prediction in hypernatraemia, although it was still not satisfyingly accurate in the individual patient.

Recently, we have shown that hypernatraemia is a frequent electrolyte disorder in the intensive care setting and associated with increased mortality and morbidity [1,3,14].

Most cases of hypernatraemia actually develop during the ICU stay, and hypernatraemia was suggested to be an indicator for the quality of medical care [3,15]. The causes for hypernatraemia in the ICU setting differ from those acquired outside the hospital. Although inadequate fluid prescription, defects in renal concentration mechanisms (i.e. diuretic therapy) and a high sodium load predominate in the hospitalized patient, extrarenal water losses were the main reasons for community acquired hypernatraemia [2]. So it was not surprising that in our study population, the patients were mostly eu- or hypervolaemic (data not shown).

All of the used formulae for the prediction of serum sodium levels are based on the same assumption, i.e. that all daily inputs and outputs of sodium/potassium and water determine the change in serum sodium. The various formulae differ only in the degree of simplification of the original formula proposed by Edelman (see the Appendix) [16]. For the total group, all currently available formulae correlated well with the measured change in serum sodium. Three of the four formulae overestimated the changes in serum sodium levels and predicted sodium levels higher than measured, whereas the new formula of EFWC underestimated the changes slightly (Figure 1). These constant over (or under) estimations could theoretically be eliminated by introducing a correction factor for each formula. But the scattering of the results is too high to make safe predictions in the individual case. In the linear regression model, we calculated an r^2 of $\sim$0.5 for all formulae, indicating that only 50% of the variability of the predicted values may be explained by the variability of measured values. For patients with hypernatraemia, the formulae are even less predictive than those for the normonatraemic patients ($r^2 \sim 0.2$). Because a maximal day-to-day deviation of $<$5 mmol/l should be demanded for the recommended correction rate of 8–10 mmol/day, currently available formulae were not accurate enough and actually could lead to severe electrolyte derangements [4]. Deviations between calculations and the observed concentrations as large as 15 mmol/l were observed, and they illustrated a range of error by which serious complications can be induced during infusion therapy. So the recommended formulae can give the physician in care a false impression of being on the safer side [4,11].

The Adrogué–Madias formula is the most frequently recommended formula in different reviews as a guide for therapy in hyper- and hyponatraemia [4,17,18]. It is quite surprising that this formula was just recently assessed for reliability in clinical practice for the first time [11]. Even more astonishing, the Barsoum–Levine and Kurtz–Nguyen formulae were assessed in hypothetical cases only. In the study of Liamis, the Adrogué–Madias formula was used to calculate the necessary volume of a sodium chloride solution to achieve a defined change in the serum sodium level. In contrast to our observation, the predicted change in serum sodium was definitely lower than the measured change 24 h after the start of therapy (151.1 $\pm$ 6.4 versus 153 $\pm$ 8.3). The patient population in this study was different from ours because most subjects were hypovolaemic (62.8%), whereas our study population was mainly eu- or hypervolaemic. The authors concluded that necessary volume for infusion therapy could be adequately calculated using the Adrogué–Madias formula, but in single cases deviations of $>$4 mmol/l during time periods of $<$24 h could be observed [11].

Why are the various formulae so inaccurate in predicting serum sodium? All mathematical calculations of water metabolism are based on major simplifications [10]. The formulae are based on the same principles that were published by Edelman in 1958 and differ only in minor aspects [16]. The formula proposed by Adrogué and Madias was designed to predict the changes of serum sodium after the infusion of 1 litre of sodium (and potassium)-containing solution [7]. Although ongoing renal or extrarenal fluid and electrolyte losses or the change in TBW (if $>$1 litre was given) was ignored in this formula, the predicted sodium levels were similar to those observed with other calculations. This is surprising since the strength of the formula is the short-time prediction of serum sodium after giving a defined fluid load because losses are less relevant during such short observation periods.

Barsoum and Levine proposed an extended Adrogué–Madias formula, which includes the ongoing losses and the net change in TBW and should predict the change in serum sodium after the infusion of a defined solution [8]. To make the formula comparable with the Nguyen–Kurtz formula, we included all the calculated sodium/potassium and volume balances (oral, intravenous, etc.) as described in the original publication. The approach to hypernatraemia by Nguyen and Kurtz avoids the simplification of the original Edelman formula made by Barsoum–Levine and uses empirical evaluated correction factors (slope and γ-intercept). The authors mentioned that these correction factors were necessary for accurate prediction of serum sodium changes. But the reliability of the slope and γ-intercept determination was recently criticized [19]. Furthermore, Nguyen and Kurtz proposed that all ongoing inputs and losses of volume and sodium/potassium via perspiration, wound drains, stool, nasogastric suction, etc. were necessary for an exact calculation [9]. This theoretical approach is correct, but not usable in the daily routine where stool collections and exact calculations of perspiration are impossible. Therefore, in our calculations, the only difference to the Barsoum–Levine formula was the slope and the γ-intercept at least.

The formula using electrolyte-free water losses (EFWC-based formula) designed by ourselves is based on the assumption that the kidney is the main regulator in water metabolism and that the primary fluid administrated on the ICU often contains no electrolyte-free water (i.e. sodium chloride 0.9%). This means that it is the response of the kidney to such a fluid load, and not the infused volume itself, that affects serum sodium levels. Obviously, these simplifications are appropriate only if major extrarenal losses of sodium and water are not present. Renal sodium/potassium and water handling was calculated by obtaining the electrolyte-free water clearance as described by Rose [20]. The EFWC depicts the loss of pure water by using the ratio of the concentration of urine sodium and potassium to serum sodium. For the EFWC-based formula, total sodium body content was assumed to be constant in relation to TBW (if no EFW was put in) and the EFWC was subtracted from the TBW to predict the change in serum sodium levels. It can be criticized that

the input of electrolyte-free water also contributes to the change in serum sodium. But the insertion of the electrolyte-free water input in our formula was associated with major deviations (>15 mmol/l) in the predicted serum sodium from the measured values (data not shown). This observation was surprising because the total electrolyte-free water intake was even high (~2000–3000 ml/day; for reasons to avoid/treat hypernatraemia) in our patients. So the electrolyte-free water intake maybe balanced by the unmeasured free water losses.

Our EFWC calculation is only partly comparable to the tonicity balance, another method for the calculation of serum sodium changes. Halperin and co-workers have shown that the calculation of EFWC offers comparable results for changes in serum sodium levels as the tonicity balance if the admitted fluid contains no electrolyte-free water [21]. Nevertheless, some information on pathophysiology will be lost by calculation of EFWC compared to the tonicity balance, which deals with total sodium/potassium and volume inputs and outputs. Our formula predicted the daily serum sodium changes equally well to the other formulae. In hypernatraemic states, the calculations were even more accurate. This may be due to the fact that the major reason for evolution of hypernatraemia in our patient group was a disturbance of the urinary concentration mechanisms. It has to be stated clearly that the EFWC-based formula was not created to have a new tool for the prediction of serum sodium changes, but to show the importance of EFWC in the pathogenesis of hypernatraemia in the ICU. Except for the Adrogué–Madias formula, all other formulae are less useful in the prediction of serum sodium, because the change in urinary composition after the introduction of a fluid therapy could not be predicted. So for the prediction of serum sodium, the former urinary composition has to be used. We recommend the calculation of EFWC in the daily routine to measure the impact of the kidney on the changes in serum sodium. If the kidney is the main contributor to hypernatraemia, it could therefore be recognized even before hypernatraemia develops.

Besides the necessary mathematical simplifications, further physiological reasons imply the inability to predict serum sodium changes by the various formulae proposed in the literature. The causes as well as the maintenance factors of hypernatraemia often change very rapidly and cannot be assessed prospectively. For instance, the impact of fluid therapy on renal sodium and water handling or the non-osmotic stimulation of vasopressin secretion presents unpredictable factors. Recent investigations have shown that sodium can be stored in the skin in an osmotically inactive form. It is not possible to predict under which circumstances how much of the infused sodium will be stored in these pools [22–24].

This retrospective analysis has some obvious methodological limitations that were necessary to simulate the daily routine. We used two major simplifications: we excluded data from severe calculable factors, such as perspiration or stool losses. Moreover, TBW was calculated using the body weight on admission. Concise evaluations of daily changes of TBW are nearly impossible in the ICU setting even if body weight is measured daily. We estimated the change of TBW by the calculation of the total daily volume balance. Additionally, formulae to guide infusion therapy in dysnatraemias remain to be tested for accuracy in a hyponatraemic collective. Because of the totally different pathophysiology of hyponatraemia, we cannot make any assumptions on the validity of the formulae in the hyponatraemic state.

We conclude that the various formulae recommended for guidance of infusion therapy for the correction of hypernatraemic states are inaccurate in the clinical setting for different reasons. Although there is a good correlation between the predicted and actual changes for the whole group, the formulae were unable to predict changes in the serum sodium level in the individual patient and thus are not without risk in practice. The analysis of major pathophysiological mechanisms (extrarenal and renal losses of electrolyte-free water, volume status, etc) that contributes to hypernatraemia was more important for therapy guidance than all the proposed formulae [21]. Integration of electrolyte-free water clearance into the calculation might improve the predictive power. However, for the daily clinical practice, as all reviews that discuss the tested formulae state, regular measurements of serum sodium and electrolyte balances are mandatory to correct dysnatraemias, to maintain normonatraemia and to avoid complications of infusion therapy.

Appendix

All of the used formulae were based on the Edelman approach that defines that the relation of the total body exchangeable sodium and potassium content to total body water determines the serum sodium level (A.7):

$$\text{(simplified formula) } \mathrm{Na} = \frac{(\mathrm{Na_e} + \mathrm{K_e})}{\mathrm{TBW}}. \qquad \text{(A.1)}$$

Therefore, $\mathrm{Na_e} + \mathrm{K_e} = \mathrm{Na} \times \mathrm{TBW}$, where $\mathrm{Na_e}$ and $\mathrm{K_e}$ represent the total exchangeable sodium and potassium content of the body, respectively. According to that only a change in $\mathrm{Na_e} + \mathrm{K_e}$ or in TBW can influence the serum sodium level:

$$\mathrm{Na_2} = \mathrm{Na_1} + \frac{\Delta(\mathrm{Na} + \mathrm{K})}{\Delta\mathrm{TBW}} \quad \text{or}$$

$$\mathrm{Na_2} = \frac{(\mathrm{Na_{e1}} + \mathrm{K_{e1}})}{\mathrm{TBW_1}} + \frac{\Delta(\mathrm{Na} + \mathrm{K})}{\Delta\mathrm{TBW}}. \qquad \text{(A.2)}$$

A.1. Adrogué–Madias formula (1)

The original equation proposed by Adrogué and Madias was designed to estimate the change in serum sodium after the infusion of 1 litre of infusate:

$$\Delta\mathrm{Na_1} = \frac{(\mathrm{Na_{inf}} + \mathrm{K_{inf}}) - \mathrm{Na_1}}{\mathrm{TBW} + 1}. \qquad \text{(A.3)}$$

To predict the effect of a certain infusion on serum sodium concentration, we used the original formula and substitute only for a variable volume of the solution [1]:

$$\mathrm{Na_2} = \frac{(\mathrm{Na_1} \times \mathrm{TBW}) + [\mathrm{Vol_{inf}} \times (\mathrm{Na} + \mathrm{K})_{\mathrm{inf}}]}{\mathrm{TBW} + \mathrm{Vol_{inf}}}. \qquad \text{(A.4)}$$

A.2. Barsoum–Levine formula [4]

The formula proposed by Barsoum and Levine is derived from the Adrogué–Madias formula. It additionally contributes to ongoing fluid and sodium/potassium gains and losses. It was designed to predict the change (ΔNa) in serum sodium concentration:

$$\Delta Na = \frac{\{(Vol_{inf} \times [Na + K]_{inf}) - (Vol_{urine} \times [Na + K]_{urine}) - (\Delta Vol \times Na_1)\}}{TBW + (\Delta Vol)}. \quad (A.5)$$

To derive the formula for predicting the new serum sodium concentration, we just have to solve the formula for ΔNa. This will result in the following equation:

$$Na_2 = \frac{(TBW \times Na_1) + [Vol_{input} \times (Na + K)_{input} - Vol_{out} \times (Na + K)_{out}]}{TBW + \Delta Vol}. \quad (A.6)$$

A.3 Nguyen–Kurtz formula [16]

In comparison to the other formulae, the Nguyen–Kurtz formula is based on the original (not simplified) formula by Edelman:

$$Na_{plasma\text{-}water} = \frac{1.11 \times (Na_e + K_e)}{TBW} - 25.6. \quad (A.7)$$

Two important factors (slope and γ-intercept) of water metabolism were included in the formula. The physiological and pathological effect of the slope (1.11) and the γ-intercept (−25.6) are discussed in detail elsewhere [15,16]. In short, the effect of the Gibbs–Donnan equilibrium and the osmotic coefficient of sodium salts were responsible for the slope of 1.11; the γ-intercept consists of the osmotically inactive exchangeable sodium and potassium, the plasma water potassium concentration and the non-sodium/non-potassium osmotically active osmoles. For the calculation of Na_{plasma} (instead of $Na_{plasma\text{-}water}$), the slope is 1.03 and the γ-intercept is 23.8.

$$Na_2 = \frac{[(Na_1 + 23.8) \times TBW] + [1.03 \times [(Na + K)_{input} - (Na + K)_{out}]]}{TBW + \Delta Vol} - 23.8. \quad (A.8)$$

A.4. Electrolyte-free water clearance formula

Our formula is based on the assumption that the loss of electrolyte-free water in the urine is the major determent for the new serum sodium concentration. In the nominator, the serum sodium concentration is multiplied by TBW to calculate the total body sodium content. The denominator consists of the subtraction of the electrolyte-free water clearance (EFWC) in the urine from TBW. The impact of the slope and the γ-intercept on the serum sodium levels was not included in the formula (see the Discussion section). The EFWC is used in contrast to the other formulae instead of the change in total exchangeable sodium and potassium as well as the change in TBW (A.8). In comparison to the Adrogué–Madias formula that ignores all outputs, our formula ignores all sodium/potassium and water inputs. This is further discussed in the main text:

$$EFWC = Vol_{urine} \times \left(1 - \frac{(Na + K)_{urine}}{Na_1}\right), \quad (A.9)$$

$$Na_2 = \frac{Na_1 \times TBW}{TBW - EFWC}. \quad (A.10)$$

Abbreviations

Na_1	serum sodium concentration day 1
Na_2	serum sodium concentration day 2
TBW	total body water: TBW calculated on the day of admission with correction based on the total daily water balance
Na_{inf} and K_{inf}	sodium and potassium concentration of the infused fluids
Vol_{inf}	volume infused in ml
Na_{input} and K_{input}	sodium and potassium concentration of all applicated fluids (oral, intravenous)
Vol_{input}	total volume input in ml (oral, intravenous)
Na_{urine} and K_{urine}	sodium and potassium concentration of the urine
Vol_{urine}	volume urine in ml
ΔVol	difference in volume between measured inputs and outputs
Vol_{out}	total volume output: urine + extrarenal fluid loss via tubes (nasogastric suction and wound drains)
$(Na+K)_{out}$	sodium and potassium concentration of extrarenal losses, calculated as a hypotonic fluid with a fixed value of 110 mmol/l

Acknowledgement. The study was performed at the Critical Care Unit 13H1, Clinic for Internal Medicine III, Medical University of Vienna.

Conflict of interest statement. None declared.

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Received for publication: 12.12.07
Accepted in revised form: 26.6.08