Hypertonic Saline for Hyponatremia: Risk of Inadvertent Overcorrection

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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.

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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.

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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.

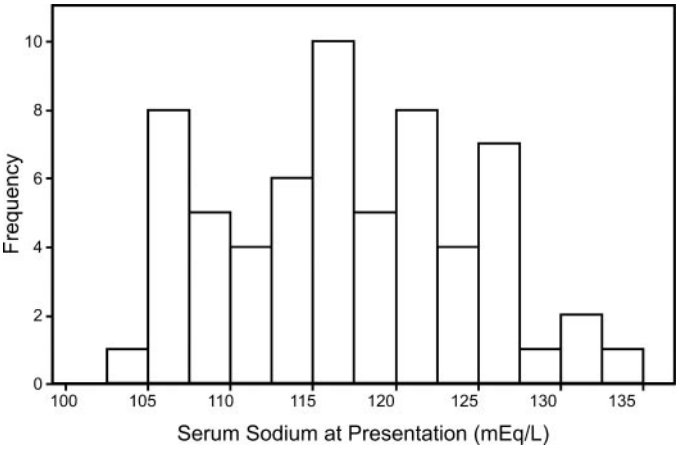

Figure 1. Distribution of serum sodium at presentation.

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

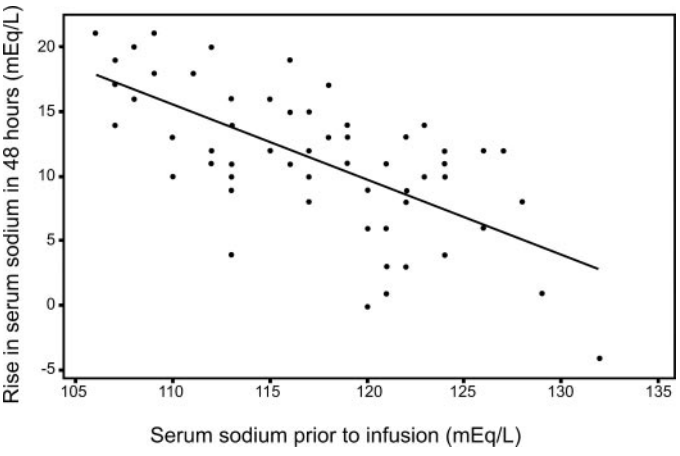

Figure 2. Relationship of rise in sodium at 48 h to preinfusion sodium concentration.

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

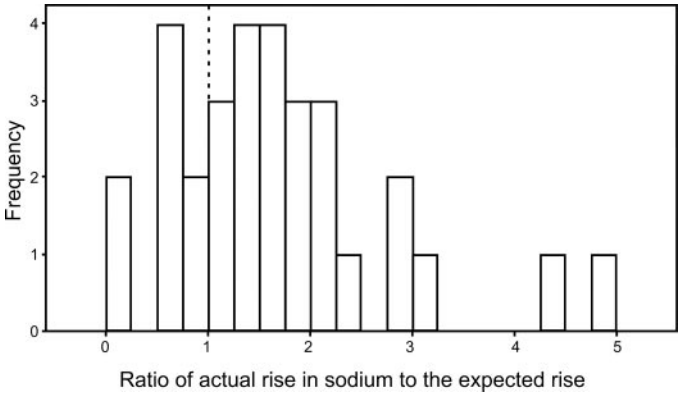

Figure 3. Ratio of actual to expected rise in sodium as calculated using the Adrogué-Madias formula. A value of 1 indicates that the entire increase in serum sodium concentration can be accounted for by the administered hypertonic saline. In 74.2% of the patients with preinfusion sodium <120 mEq/L, the 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

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Disclosures

None.

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