AJKD
Original Investigation

Hypertonic Saline and Desmopressin: A Simple Strategy for Safe Correction of Severe Hyponatremia

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Background: Prompt correction of severe hyponatremia is important, but correction also must be limited to avoid iatrogenic osmotic demyelination. Expert opinion recommends that serum sodium level not be increased by more than 10-12 mEq/L in any 24-hour period and/or 18 mEq/L in any 48-hour period. However, inadvertent overcorrection is common, usually caused by the unexpected emergence of a water diuresis.

Study Design: Quality improvement report.

Setting & Participants: All 25 patients admitted to a community teaching hospital between October 1, 2008, and September 30, 2011, who were treated for serum sodium level <120 mEq/L with concurrently administered desmopressin and hypertonic saline solution.

Quality Improvement Plan: Concurrently administered desmopressin (1-2 μg parenterally every 6-8 hours) and hypertonic saline with weight-based doses adjusted to increase the serum sodium concentration by 6 mEq/L, avoiding inadvertent overcorrection of severe hyponatremia.

Outcomes: Rate of correction of hyponatremia, predictability of response to the combination, adverse events related to therapy.

Measurements: Rate of correction of hyponatremia at 4, 24, and 48 hours; administered dose of 3% saline solution, salt tablets, and potassium; predicted increase in serum sodium level.

Results: Mean changes in serum sodium levels during the first and second 24 hours of therapy were 5.8 $\pm$ 2.8 (SD) and 4.5 $\pm$ 2.2 mEq/L, respectively, without correction by >12 mEq/L in 24 hours or >18 mEq/L in 48 hours and without a decrease during therapy. There was no significant difference between actual and predicted increases during the first 24 hours. There was no adverse effect associated with therapy.

Limitations: Without concurrent controls, we cannot be certain that outcomes are improved. Balance studies were not performed.

Conclusions: Combined 3% saline solution and desmopressin appears to be a valid strategy for correcting severe hyponatremia, but studies comparing the regimen with other therapeutic strategies are needed.
Am J Kidney Dis. 61(4):571-578.

INDEX WORDS: Hyponatremia; desmopressin; hypertonic saline; syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

The management of severe hyponatremia can be challenging. Prompt correction is important to avoid morbidity and mortality from the untreated electrolyte disturbance, but correction also must be limited to avoid iatrogenic osmotic demyelination. Expert opinion recommends that serum sodium concentration not be increased by more than 10-12 mEq/L in any 24-hour period and/or 18 mEq/L in any 48-hour period.[1,2] However, inadvertent overcorrection is common, especially when serum sodium level is less than 120 mEq/L, and it usually is caused by the unexpected emergence of a water diuresis.[3]

Recently, our group reported a novel strategy to achieve controlled correction of hyponatremia.[4] A patient with a serum sodium level of 96 mEq/L was successfully managed with the combined administration of 3% saline solution and desmopressin. Hypertonic saline solution was given to ensure a prompt and reliable increase in serum sodium level while desmopressin was given to prevent a free water diuresis from emerging when the causes of the patient's hyponatremia (hypovolemia, thiazide diuretics, and a selective serotonin reuptake inhibitor) had been removed. Desmopressin was given immediately, without waiting for urine output to increase, a change from the often unsuccessful wait-and-react strategy we had been using earlier.

Subsequently, we adopted this strategy more routinely in managing all patients with serum sodium level less than 120 mEq/L. All nephrologists at our hospital are part of the same group. Although no formal protocol was used, members of the group built on the experience of their colleagues, and a standard therapy gradually emerged. The present study was undertaken to report our experience with the strategy.

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Received August 10, 2012. Accepted in revised form November 6, 2012. Originally published online December 26, 2012.

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0272-6386/$36.00
http://dx.doi.org/10.1053/j.ajkd.2012.11.032

METHODS

Following institutional review board approval, we conducted a retrospective chart review from a single-center 523-bed community teaching hospital. Medical records of all patients admitted between October 1, 2008, and September 30, 2011, who received desmopressin and hypertonic saline solution during the same hospitalization were reviewed. Twenty-five patients older than 18 years with a serum sodium level <120 mEq/L who received desmopressin before or within 1 hour of hypertonic saline solution administration were identified. Our hospital's nephrology group was involved in the management of all these cases. None of the patients enrolled in our series has been reported previously in other studies.

Aware of our previous case report,[4] each nephrologist calculated the total amount of hypertonic saline that would increase serum sodium level by ~6 mEq/L in 24 hours and in some cases, chose a more rapid initial infusion rate or a 50- to 100-mL bolus (for seizures and coma) based on his/her clinical assessment of the severity of the patient's presenting symptoms; the infusion rate was then titrated based on serum sodium results to achieve the desired goal. Desmopressin was administered prior to the initiation of hypertonic saline, and the dose varied from 1-2 μg (based on individual preference) at approximately 6- to 8-hour intervals either intravenously or subcutaneously, except for one patient weighing 120 kg who was given 4 μg. Because there was no formal protocol, some of the nephrologists decided to reduce the frequency and/or dosage of desmopressin after the first 24 hours, while others maintained the same dose throughout the infusion. Urine output was monitored every 8 hours and serum sodium concentration every 4-6 hours.

To determine dose-response relationships, we determined the increase in serum sodium level prior to the start of the hypertonic saline solution infusion to the closest values 4, 24, and 48 hours later. As in our previous study reporting on the use of hypertonic saline solution alone,[3] we calculated the predicted response to our current therapy with a commonly used formula[5]:

$$\Delta sNa = \frac{(513 - sNa_0) \times \text{number of liters of 3\% saline solution}}{(\text{Total body water} + 1)}$$

where sNa_0 is serum sodium concentration (in milliequivalents per liter) before initiation of hypertonic saline solution infusion. Total body water (in liters) was calculated using the Watson formula.[6] Salt tablets and/or potassium were converted to 3% saline solution equivalents as follows: (1) 1 g of salt tablets was taken to equal 34 mL, and (2) 1 mEq of either oral potassium chloride elixir or 400 mmol/L of intravenous potassium chloride was taken to equal 2 mL. The response to 3% saline solution infusion predicted by the formula was compared to the actual response 24 and 48 hours after starting 3% saline solution infusion. Data are depicted as mean ± standard deviation. Differences between mean values were determined by Wilcoxon rank sum test.

RESULTS

Demographics

Patients ranged in age from 46 to 90 years and older, with 20% older than 86 years and 56% women. The cause of hyponatremia usually was multifactorial, with most cases related to medications (Table 1). A history of congestive heart failure was recorded in at least 45% of cases, but no patient had decompensated heart failure at the time of presentation with hyponatremia; 8% had chronic kidney disease and 8% had postoperative hyponatremia. Although 16% were asymptomatic, most patients presented with hyponatremic symptoms: 16% were awake but confused, 12% were comatose, 8% had seizures, and the rest had nonspecific symptoms such as nausea, malaise, and/or an unsteady gait.

Dosing

During the first 24 hours, desmopressin dose was 2 μg in most patients (84%), 1 μg in 3 patients, and 4 μg in 1 patient, usually given at 8-hour intervals (68% of patients), subcutaneously (60%) or intravenously. In 19 patients, desmopressin treatment was continued for at least another 24 hours at a decreased dose in 2 patients and less frequently in 9 patients.

During the first 24 hours of therapy, an average of 6.2 (range, 1.2-11) mL/kg of 3% saline solution was administered. The rate of infusion tended to be more rapid during the first 4 hours than in the subsequent 20 hours, and an initial bolus of 3% saline solution was given to patients with more severe symptoms: 50 mL (n = 3) and 100 mL (n = 2; Table 2). Potassium was given to 8 patients during the first 24 hours of therapy and to 7 in the second 24-hour period. Salt tablets were given to 3 and 5 patients in the first and second 24-hour periods, respectively. On average, serum sodium was measured every 4 hours in the first 24 hours and less often thereafter. Furosemide was not given to any patient during the first 24 hours, and it was given to 2 of the 25 patients during the second 24 hours of the protocol.

Response to Treatment

The mean increase in serum sodium levels during the first 24 hours of therapy was 5.8 ± 2.8 mEq/L, and it was 2.6 ± 2.0 mEq/L during the first 4 hours. In patients 14 and 19, serum sodium levels decreased by 2 and 1 mEq/L, respectively, in the first 4 hours. In patient 14, there was a 4-hour delay between the first dose of desmopressin and the start of 3% saline solution infusion, whereas in patient 19, serum sodium level had already increased by 8 mEq/L by autocorrection before the regimen was started. During the second 24 hours, the increase was 4.5 ± 2.2 mEq/L. No patient had correction by >12 mEq/L in 24 hours or >18 mEq/L in 48 hours (Figs 1 and 2). However, patients 9 and 19 had correction by 10 mEq/L in 24 hours, and patient 1, by 11 mEq/L, rates that we would consider excessive. In both cases with correction by 10 mEq/L, 80-120 mEq of potassium was given without an appropriate decrease in the rate of 3% saline solution infusion. One of these patients received only 1 μg of desmopressin and may not have had adequate antidiuresis. The single patient whose correction

Table 1. Patient Characteristics

Pt No.	Age (y)/Sex	eGFR (mL/min/1.73 m^2)	sNa (mEq/L)	uOsm (mOsm/L)	Medications	Persistent SIADH	Transient SIADH	Other Factors
1	56/M	133	112	515		Adenocarcinoma of the lung	Hypoxia	
2	56/F	109	114	579			Alcohol withdrawal	Poor solute intake
3	67/F	109	109	NA		Chronic lung dis	Pneumonia, nausea	Poor solute intake
4	≥90/M	38	108	256	Furosemide			Excessive diuresis for CHF, diarrhea
5	≥90/F	77	117	NA	Thiazide		Nausea	Poor solute intake
6	54/M	101	115	399	Thiazide & carbamazepine		Pain	
7	69/M	96	118	325	Thiazide		Pain	Poor solute intake
8	52/M	125	110	345	Olanzapine	Chronic lung dis		Poor solute intake
9	63/F	60	109	304	Thiazide		Pain	
10	45/F	125	105	353	SSRI	SCLC	Nausea	
11	76/F	89	118	NA	Thiazide			Poor solute intake
12	63/M	121	113	606		SCLC		Poor solute intake (uNa = 11 mEq/L)
13	46/M	185	108	427		Chronic lung dis	Pneumonia	Beer potomania
14	77/F	71	112	350	SSRI		Pain	Adenocarcinoma
15	84/F	103	112	646	Thiazide			
16	≥90/F	50	111	582	Thiazide		Postop, pain, nausea	
17	74/F	132	111	364	Thiazide	Dementia		Hypertensive emergency
18	73/F	114	118	NA		Chronic lung dis	Pneumonia	Poor solute intake
19	80/F	86	113	NA	Thiazide		Nausea, pain	
20	85/M	26	117	539	Thiazide & SSRI		Postop, pain, nausea	CKD
21	≥90/F	41	113	NA	Thiazide		Nausea	Poor solute intake, volume depletion
22	51/M	109	110	NA				Sweating, polydipsia, poor solute intake
23	62/F	79	118	NA				Volume depletion, poor solute intake
24	62/M	96	107	NA	Carbamazepine		Pain, panhypopituitarism	
25	≥90/M	88	117	514	Thiazide		Pain	Diuretic, poor solute intake

Abbreviations and definitions: CHF, congestive heart failure; CKD, chronic kidney disease; dis, disease; eGFR, estimated glomerular filtration rate; NA, not available; Postop, postoperative; Pt, patient; SCLC, small cell lung cancer; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; sNa, lowest pretreatment serum sodium concentration; SSRI, selective serotonin reuptake inhibitor; uNa, urine sodium concentration; uOsm, pretreatment urine osmolality.

was >10 mEq/L continued to receive hypertonic saline solution for 5 hours after the day's correction had already reached 6 mEq/L, a deviation from the intended protocol.

Urine output while receiving the combined regimen averaged 1,320 (range, 250-4,115) mL per 24 hours. Urine osmolality was not measured consistently during the administration of desmopressin.

Predictability of the Regimen

A modified Adrogué-Madias equation was used to predict the increase in serum sodium level depending on the amount of hypertonic saline solution, potassium, and salt tablets given during the study period. The differences between the actual and predicted increases in serum sodium level during the first and second 24 hours of the combined desmopressin and hypertonic saline solution infusions are shown on Bland-Altman plots[7] (Figs 3 and 4). The actual and predicted increases in serum sodium levels during the first 24 hours did not differ significantly (5.8 ± 2.8 vs 5.5 ± 3.3 mEq/L; $P = 0.7$). However, for the 19 patients who continued to receive 3% saline solution for at least an additional 24 hours, the difference

Table 2. Rate of Serum Sodium Concentration Correction and Dosage of Medications

	Serum Sodium (mEq/L)			Total Desmopressin Dose (μg)		3% Saline Solution Dose		
Patient No.	Baseline	24 h	48 h	First 24 h	Second 24 h	Initial (mL/h)	First 24 h (mL/kg)	Second 24 h (mL/kg)
1	112	123	125	4	1	25	7.1	0.0
2	116	122	126	12	8	100 (bolus)	3.8	0.0
3	109	116	122	4	6	10	7.3	5.2
4	108	115	121	8	1	25	7.9	2.3
5	117	123	128	6	6	40	2.9	4.8
6	115	117	121	4	4	20	4.3	6.8
7	118	123	125	6	0	35	7.7	0.0
8	110	118	127	6	6	25	2.4	5.9
9	110	117	122	6	6	30	8.6	3.0
10	106	110	114	6	3	50 (bolus)	4.8	2.5
11	118	124	124	4	4	20	4.6	2.0
12	114	121	124	6	6	25	2.2	3.9
13	108	114	118	3	2	20	11.1	2.6
14	114	117	125	4	6	20	1.3	4.9
15	113	118	123	3	2	25	5.9	1.8
16	113	117	124	3	3	25	6.5	10.0
17	113	118	123	6	6	50 (bolus)	18.8	6.7
18	118	123	125	6	4	15	3.6	0.0
19	121	129	131	6	0	30	8.6	0.0
20	117	124	129	3	3	30	3.0	5.6
21	118	129	131	6	4	20	10.2	0.0
22	112	122	127	4	3	20	3.5	1.8
23	118	121	124	5	1.5	50 (bolus)	8.8	4.9
24	112	113	120	6	6	100 (bolus)	3.5	2.3
25	118	118	125	6	4	20	6.6	6.6

Note: Time refers to therapy initiation; thus, baseline is before starting therapy.

between the actual and predicted increases was significant (4.9 ± 2.1 vs 3.7 ± 2.4 mEq/L; $P = 0.05$). A higher than expected increase in serum sodium level during the second 24 hours might be attributed to the diminished dose of desmopressin used in some patients. However, the same phenomenon appeared to occur in the 13 patients whose desmopressin dose in the second 24 hours was unchanged. In these 13 cases, actual correction did not differ significantly from the predicted value in the first 24 hours (4.7 ± 2.5 vs 5.4 ± 4.0 mEq/L; $P = 0.7$) or in the second 24 hours (5.7 ± 1.7 vs 4.5 ± 2.6 mEq/L; $P = 0.1$), but there

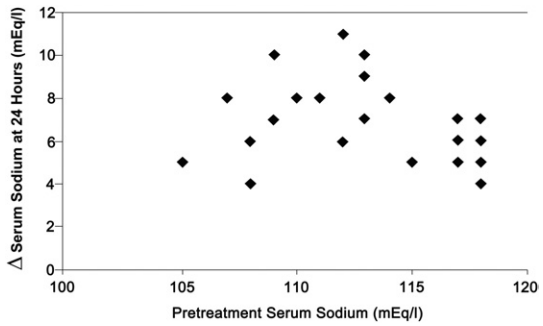

Figure 1. Increase in serum sodium concentration during the first 24 hours. Pretreatment serum sodium is the lowest serum sodium level recorded before therapy began and increase in serum sodium level is the largest increase recorded during the ensuing 24 hours.

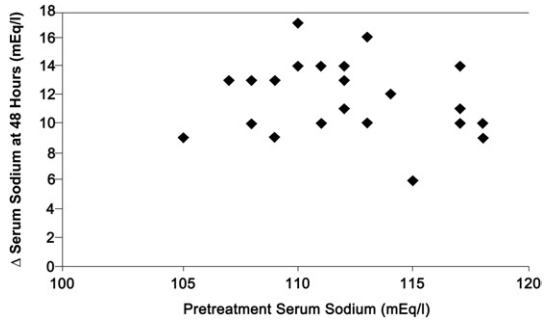

Figure 2. Increase in serum sodium concentration during the first 48 hours. Pretreatment serum sodium is the lowest serum sodium level recorded before therapy began and increase in serum sodium level is the largest increase recorded during the ensuing 48 hours.

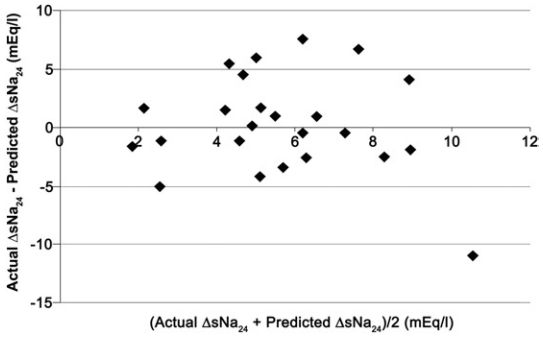

Figure 3. Bland-Altman plot comparing actual and predicted increases in serum sodium concentration (ΔsNa_{24}) in the first 24-hour period.

was a trend toward greater correction in the second period.

Patient 17, who had idiopathic syndrome of inappropriate secretion of antidiuretic hormone (ADH), had correction by much less than predicted (5 vs 16 mEq/L). During the first 24 hours, in addition to hypertonic saline solution, she received >3 L of fluid in intravenous medications, isotonic saline solution, and tube feeds; her urine output was larger than for any other patient (4.1 L).

Complications of Therapy

Infusion of 3% saline solution in a large peripheral vein was well tolerated and there was no report of pain requiring discontinuation of the infusion and no extravasation injuries. Despite the high degree of cardiac burden, only one patient developed clinically apparent congestive heart failure during the course of therapy. The patient, who had pre-existing severe mitral stenosis, developed rapid atrial fibrillation and radiographic evidence of heart failure that responded quickly to diuretic treatment. The mitral valve was replaced surgically (as had been planned) after correction of hyponatremia. No patient experienced neurologic complications during the hospitalization.

DISCUSSION

In this retrospective review of patients in our institution presenting with severe hyponatremia and treated with concurrent infusion of 3% saline solution and desmopressin, we demonstrate that this proactive approach was safe, feasible, and effective. Dosing desmopressin at 2 μg every 8 hours appears to achieve a predictable and controlled response, with little advantage to lower dosages.

Correction of severe hyponatremia is challenging. The primary complication of correction is osmotic demyelination syndrome, a devastating condition characterized clinically by severe and often irreversible neurologic deterioration that occurs 2-7 days after treatment.[1] Slow correction of hyponatremia will largely prevent osmotic demyelination syndrome. We and others advocate a goal rate of correction of 6 mEq/L of serum sodium level per day, a conservative rate that will allow for a safety net even if exceeded.[8]

Although many experts agree with the appropriateness of this goal, there is considerably less clarity in how to best approach the actual management of the correction. A primary challenge to achieving a slow sustained increase in sodium level is the heterogeneity of the patient population and cause of the hyponatremia (Table 1). Some patients will present with readily reversible conditions and experience a rapid decrease in circulating ADH level and subsequent water diuresis that has the potential to increase serum sodium level rapidly past the safe rate. These include medication-induced hyponatremia (especially thiazides and selective serotonin reuptake inhibitors), hypovolemia, pain, nausea, or a combination of these. Other patients will maintain concentrated urine and are resistant to correction. It is not uncommon for patients with severe hyponatremia to present with multiple confounding risk factors, mental status changes that limit the utility of the history, and subtle or even contradictory findings on physical examination or laboratory analysis that make estimation of volume status difficult. Experienced clinicians realize that when the cause is unclear, the clinical course will be unpredictable. The most widely used approach, summarized in a recent review, is to choose between isotonic or hypertonic saline solution depending on symptoms and volume status, monitor the patient carefully, and then respond to impending or actual overcorrection or to symptoms of osmotic demyelination syndrome with administration of electrolyte-free water or desmopressin.[9] We have found that responding to water diuresis with the timely administration of 5% dextrose in water is difficult to achieve in practice. In our hands, this strategy led to overcorrection in ~10% of patients with serum sodium levels <120 mEq/L treated with 3% saline solution.[10] Similarly, in a series of

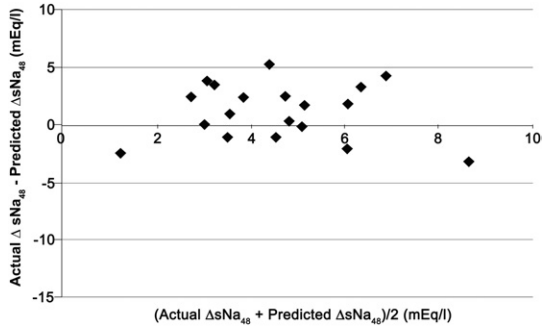

Figure 4. Bland-Altman plot comparing actual and predicted increases in serum sodium concentration (ΔsNa_{48}) in the second 24-hour period.

Table 3. Comparison of Various Strategies Used for the Correction of Hyponatremia

Therapeutic Strategy	Advantages	Disadvantages
Hypertonic saline solution	Reliably increases serum sodium, readily available, inexpensive	Unpredictable with frequent inadvertent overcorrection, fluid overload
Isotonic saline solution	Familiarity, readily available, inexpensive	Does not reliably increase serum sodium, unpredictable with frequent inadvertent overcorrection, fluid overload
Urea	Reliably increases serum sodium, possible protection against osmotic demyelination syndrome, avoids fluid overload, inexpensive	Unfamiliarity, not commercially available in US, unpredictable with frequent inadvertent overcorrection
"Vaptans"	Avoids fluid overload	Does not reliably increase serum sodium, unpredictable, hypotension, expense
Hypertonic saline solution and desmopressin	Reliably increases serum sodium; readily available; preemptively prevents water diuresis, decreasing risk of inadvertent overcorrection; does not depend on cause of hyponatremia	Unfamiliarity, fluid overload

patients treated at our hospital with either 0.9% or 3% saline solution for serum sodium level <120 mEq/L, reactive rather than proactive use of desmopressin successfully avoided correction by >18 mEq/L in 48 hours, but one-third experienced correction by ≥12 mEq/L in the first 24 hours before desmopressin could be administered.[10]

"Vaptans" have documented efficacy in the correction of mild to moderate hyponatremia and have not been associated with osmotic demyelination to date. However, the limited experience of their use in the setting of severe chronic hyponatremia shows that these agents have the potential to induce overcorrection with water diuresis that may be difficult to reverse. A study evaluating the effectiveness of intravenous conivaptan found that 16.7% of patients had correction by >12 mEq/L in the first 24 hours, with all 6 patients with a serum sodium level <120 mEq/L experiencing excessive correction.[11]

The response to urea, which has been used in Belgium to correct severe hyponatremia, is not predictable because the increase in serum sodium level depends on urea excretion, which would be expected to vary with volume status and ADH level. In a study reporting on the use of intravenous or oral urea to treat patients with a serum sodium level <115 mEq/L, more than one-third of patients with a serum sodium level <120 mEq/L had excessive correction.[12] Urea is not readily available for clinical use in the United States.

Our approach with concurrent 3% saline solution administered with desmopressin offers an effective alternative to the traditional watchful waiting approach, with advantages and disadvantages of other strategies summarized in Table 3. By negating the possibility of a large decrease in ADH level on renal water handling, the clinician takes control over confounding causes and their influence on the amount and timing of aquaresis. The preemptive approach was embraced enthusiastically by our own nephrologists, who found it less labor intensive and more predictable than the reactive strategy. By simultaneously adding sodium and potassium, a controlled increase is possible. In the process, absolute estimates of volume status, nebulous as they are, are replaced with the much simpler monitoring for fluid overload, targeting the need, if any, to add diuretics during the infusion. The approach creates the opportunity for a more standardized protocol whereby the clinical courses of patients with hyponatremia of diverse causes are forced into a more predictable pattern.

This approach seems particularly suited for patients for whom history or physical examination findings are challenging to interpret or are in conflict and in patients with an obviously reversible cause, such as diuretic-induced hyponatremia. There are patients for whom our approach is neither advantageous nor desirable. For example, administration of desmopressin to psychotic patients with acute self-induced water intoxication is potentially hazardous (should the patient ingest additional water while water excretion is impaired) and usually unnecessary (because autocorrection of short-lived hyponatremia is usually well tolerated). The regimen also is ill suited for severely

edematous patients with hyponatremia caused by heart failure or hepatic cirrhosis.

A recent review raised concerns about the concurrent administration of 3% saline solution and desmopressin, and our data are able to allay some of these.[9] One concern was that the approach might increase the risk of hyponatremia from fluid in medications and tube feedings. We agree that this is a concern in all patients with hyponatremia and even more so in patients receiving desmopressin. None of our patients experienced a decrease in serum sodium level in a 24-hour period, but in one patient, serum sodium level increased by much less than would be predicted, in part because of free water contained in medications and tube feeds. In addition, one patient experienced a 2 mEq/L decrease in serum sodium level because desmopressin and 3% saline solution were not started at the same time.

Another concern was that desmopressin might be administered to patients who may already have high circulating ADH levels. We do not believe this to be a serious problem. If the patient has high levels of endogenous ADH, exogenous desmopressin will not influence water excretion or the rate of correction, but we know of no evidence that this would be harmful. More importantly, the presence of exogenous desmopressin ensures constant rates of water loss, should endogenous secretion decrease or cease. Our protocol uses a modest amount of desmopressin for only 2-3 days.

There is a fear of fluid overload and hypoxia as a result of the 3% saline solution, particularly when given with desmopressin. This is a valid concern for all patients receiving 3% saline solution, and close clinical observation is required in all patients. When indicated, patients at risk of fluid overload can be given furosemide. Our review highlights that the routine use of this combination was not associated with any episodes of severe or even clinically significant heart failure attributable to fluid overload despite a nonselected population with a large number of elderly patients with heart disease. One case of radiographic pulmonary edema was observed in a patient with pre-existing severe mitral stenosis and rapid atrial fibrillation. The infrequency of complications may be due to the limited correction goals; to achieve the desired 6-mEq/L correction in a 60-kg woman, only 450 mL of 3% saline solution would be required, an amount that would cause as much volume expansion as 1.5 L of isotonic saline solution.

In the past, some pharmacy literature has advocated infusion of hypertonic saline solution in a central rather than a peripheral vein, citing risks of venous sclerosis and extravasation injury. We administered hypertonic saline solution peripherally, and none of our patients experienced these complications. In reviewing the literature, we were unable to find data supporting the need to infuse 3% saline solution centrally, and the most recent edition of a standard pharmacy reference work no longer mandates infusion in a central vein.[13]

Concurrent replacement of potassium deficits during the administration of 3% saline solution can result in inadvertent excessive correction. Because serum sodium level is a function of the sum of exchangeable sodium and potassium, the increase in serum sodium level caused by 1 mEq of potassium is equivalent to that caused by 1 mEq of sodium. If large doses of potassium are required, serum sodium level can increase enough to cause osmotic demyelination.[14] Therefore, during potassium administration, the rate of 3% saline solution infusion should be slowed proportionally. For example, if a patient receiving 3% saline solution at 20 mL/h is given 20 mEq of potassium chloride orally or in a 400-mmol/L intravenous solution, the saline solution infusion should be discontinued for 2 hours (20 mEq of potassium chloride is equivalent to 40 mL of 3% saline solution). Administration of hypotonic 100 mmol/L of potassium chloride does not require an adjustment in the rate of 3% saline solution infusion.

With time, the response to 3% saline solution might be expected to diminish as more of the infused sodium is excreted in hypertonic urine in response to volume expansion, a phenomenon known as "desalination."[15] Although this was not a problem for most of our patients, it should be watched for, and upward titration of the dose of 3% saline solution sometimes may be necessary. For one patient whose serum sodium level increased far less than would be predicted, desalination may have had a role. However, for most of our patients, the response to 3% saline solution was enhanced in the second 24 hours of infusion, so that unlike the first 24 hours, the actual increase in serum sodium level significantly exceeded the expected increase. Without continuous monitoring of urine osmolality and urine sodium and potassium losses, we can only speculate about why this occurred. Equating sodium chloride tablets and oral potassium chloride to 3% saline solution underestimates the expected correction because these do not contain as much water as hypertonic saline solution. However, modifying the calculation to take this into account did not change the result. Increasing water losses due to partial escape from the antidiuretic effect of desmopressin and/or recovery of lost intracellular osmolytes would explain the finding.

Although the response to 3% saline solution is relatively predictable when desmopressin is used to prevent water diuresis, it is still advisable to carefully

monitor serum sodium level at a minimum of every 6 hours. By titrating the dose and stopping therapy whenever a 6-mEq/L increase in serum sodium level is achieved, it should be possible to avoid both inadequate and excessive correction.

In conclusion, combined infusion of 3% saline solution and desmopressin appears to be a valid strategy for correcting severe hyponatremia effectively and safely. This approach appears to reduce the chance of inadvertent overcorrection. It still requires substantial oversight by the nephrologist, who must identify patients who are poor candidates for the protocol, such as those at risk of inadvertent exacerbation of hyponatremia (eg, due to psychotic water drinking) and those whose response to desmopressin will not avoid inadvertent overcorrection (eg, due to a solute diuresis from urea or glucose). Careful balance studies to better understand the response to 3% saline solution when it is given concurrently with desmopressin and studies comparing the regimen with other therapeutic strategies are needed.

ACKNOWLEDGEMENTS

Preliminary findings of this study were presented previously at the American Society of Nephrology's Kidney Week, November 8-11, 2011 in Philadelphia, PA.

The authors acknowledge the help of Ana Espinosa, MD, in preparing the manuscript and the care provided to patients in this case series by other members of our nephrology group: Paul Bernstein, MD, Jonathan Bress, MD, Sreedevi Chennupati, MD, Marvin Grieff, MD, and Maria Rojas, MD.

Support: None.

Financial Disclosure: The authors declare that they have no relevant financial interests.

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