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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.
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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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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