Management of Severe Hyponatremia: Infusion of Hypertonic Saline and Desmopressin or Infusion of Vasopressin Inhibitors?

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Antonios H. Tzamaloukas, MD, Joseph J. Shapiro, MD, Dominic S. Raj, MD, Glen H. Murata, MD, Robert H. Glew, PhD and Deepak Malhotra, MD, PhD

Abstract: Rapid correction of severe hyponatremia carries the risk of osmotic demyelination. Two recently introduced methods of correction of hyponatremia have diametrically opposite effects on aquaresis. Inhibitors of vasopressin V2 receptor (vaptans) lead to the production of dilute urine, whereas infusion of desmopressin causes urinary concentration. Identification of the category of hyponatremia that will benefit from one or the other treatment is critical. In general, vaptans are effective in hyponatremias presenting with concentrated urine and, with the exception of hypovolemic hyponatremia, can be used as their primary treatment. Desmopressin is effective in hyponatremias presenting with dilute urine or developing urinary dilution after saline infusion. In this setting, desmopressin infusion helps prevent overcorrection of the hyponatremia. Monitoring of the changes in serum sodium concentration as a guide to treatment changes is imperative regardless of the initial treatment of severe hyponatremia.


Hyponatremia is considered severe when serum sodium concentration ([Na]) is <125 mmol/L and/or when hypertonic or isotonic saline is infused to correct severe neurological manifestations or symptomatic hypovolemia. In severe cases of hyponatremia, the rate of correction of [Na] is critical for prevention of either prolonged brain edema or osmotic demyelination. The current standard is a controlled rate of rise in [Na]. Although there is some debate about how rapid the initial increase in [Na] should be in severe hyponatremia, there is strong evidence that the incidence of osmotic demyelination increases sharply if the correction exceeds 20 mEq/L in the first 24 hours. Based on these observations, most experts recommend slower rates of correction. Recent guidelines from an expert panel recommend a minimum rate of correction of [Na], by 4 to 8 mEq/L per day, and a goal of 4 to 6 mEq/L per day if the risk of osmotic demyelination syndrome is high. The expert panel set also upper limits in the rate of correction. [Na] should not rise by more than 8 mEq/L in any 24-hour period if the risk of osmotic myelinolysis is high and by no more than 10 to 12 mEq/L in any 24-hour period or 18 mEq/L in any 48-hour period if the risk of osmotic myelinolysis syndrome is not high.

Achieving the desired rate of correction of [Na], is a difficult task. In a recent report, the rise in [Na], in the first 24 hours of treatment exceeded 12 mEq/L in 11% of the subjects admitted with severe hyponatremia. Saline infusion carries special risks of overcorrection of hyponatremia. The volume of infused saline is calculated by formulas that take into account the starting and target [Na] values, the concentration of sodium in the infused and the volume of body water before the start of saline infusion. Lack of precision, or inaccuracy, of the clinical estimates of body water entered in the formulas used to calculate the volume of infused saline required for a specific rise in [Na], are important sources of error in the predictive formulas.

The major source of error during treatment of hyponatremia with saline infusion, however, is not accounted for in the predictive formulas. The source of this error is the volume and the concentrations of sodium and potassium of the urine during the treatment period. Two recently proposed strategies addressed specifically the effect of urine volume and composition on [Na], during treatment of severe hyponatremia. These strategies, which include use of V2 vasopressin receptor inhibitors (vaptans) and infusion of desmopressin along with saline, have diametrically opposite effects on urinary free water excretion. Vaptans increase water loss in the urine (aquaresis) without changing urinary excretion of sodium or potassium; in contrast, desmopressin promotes water reabsorption in the collecting ducts, thereby limiting urinary water loss.

It is therefore imperative to analyze the advantages, risks, indications and contraindications of these 2 treatments for the various categories of hyponatremia. The recent guidelines address some of the uses of vaptans and desmopressin in hyponatremia. The purpose of this report was to provide a rationale, based on the pathogenetic mechanism of each episode of severe hyponatremia, for choosing vaptans or desmopressin plus saline as the method of treatment of severe hyponatremia. We do not address alternative methods (eg, restriction of fluid intake, administration of other than vaptan medications blocking the effect of vasopressin on the urinary concentrating mechanism, urea infusion), all of which may have a role in the management of severe hyponatremia in particular individuals.

RELATIONSHIP BETWEEN URINE COMPOSITION, URINE FLOW RATE AND CORRECTION OF [Na]—As we have previously discussed, the changes in [Na] can be predicted based on various clinical parameters, including initial body water volume, urine flow rate and electrolyte composition, infuses volume and composition as well as dietary

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ingestion and extrarenal salt and water losses. If we ignore extrarenal losses, the final serum sodium concentration after infusion of saline ([Na]_{\text{fin}}) is predicted by the equation:

\[
[Na]_{\text{fin}} = \frac{\text{TBW}_{\text{ini}} \times [Na]_{\text{ini}} + 1.11 \times V_{\text{inf}} \times [Na]_{\text{inf}} - V_{\text{urine}} \times \left\{ [Na]_{\text{urine}} + [K]_{\text{urine}} \right\}}{\text{TBW}_{\text{ini}} + V_{\text{inf}} - V_{\text{urine}}},
\]

where TBW_{\text{ini}} is total body water before the infusion, [Na]_{\text{ini}} is the initial serum sodium concentration, 1.11 is an empiric correction term proposed by Edelman et al., V_{\text{inf}} is the volume of the infusate, [Na]_{\text{inf}} is the sodium concentration in the infusate, V_{\text{urine}} is the volume of urine and [Na]_{\text{urine}} and [K]_{\text{urine}} are the concentrations of sodium and potassium in the urine, respectively.

Using this formula and assuming starting points attributable to a 70-kg man with a serum sodium of 125 mEq/L, we performed simulations shown in Figure 1. Reviewing these figures, it seems very clear that infusion of substantial amounts of hypertonic saline would be associated with very high rates of rise in [Na]_{s} unless the urine remained very concentrated. Ergo, it would be predicted that the combination of vaptan therapy, which would cause the elaboration of dilute urine, and hypertonic saline would likely result in too-rapid rates of correction. Vaptans or desmopressin are indicated in certain categories of hyponatremia and are contraindicated or ineffective in other categories.

**CATEGORIES OF HYPNATREMIA**

One large group of hyponatremias is characterized by high serum vasopressin levels and urine osmolality levels that...
are higher than the levels that should normally accompany low \( [Na] \) levels. High levels of serum vasopressin are the main cause of the inability to excrete water in this group, which consists of 3 categories, hypovolemic, euvoilemic and hyper-volemic hyponatremia.\(^7,12\)

Characterization of volume status in hyponatremic patients with high levels of serum vasopressin is critical but encounters serious difficulties. Historical evidence, clinical examination and certain laboratory findings have traditionally been the cornerstone of this classification.\(^2,7,10,12-14\) Hypovolemic hyponatremia is characterized by history suggesting loss of volume through the gastrointestinal tract, the kidneys or the skin, clinical findings (recent weight loss, orthostatic hypotension, orthostatic tachycardia, absence of edema) and low sodium concentration in the urine except when sodium losses occur through the urine.\(^7,12,13\) Euvolemic hyponatremia is characterized by the absence of historical or clinical findings of volume deficit and, usually, by relatively high urine sodium concentration and low serum uric acid level.\(^2,12,13\) Hypervolemic hyponatremia is characterized by the presence of a disease causing sodium retention, absence of clinical signs of volume deficit, significant edema (≥0.5 cm of pressure-induced edema) and low urine sodium concentration.\(^7,12,13\)

The sensitivity and specificity of clinical criteria in differentiating between hypovolemic and euvoilemic hyponatremia are poor.\(^14\) Urine sodium concentration is low in hypovolemic hyponatremia except in patients with renal losses of sodium caused by disease or diuretics. Whereas, urine sodium is high in most patients with euvoilemic hyponatremia except those who experience sodium losses in addition to the primary condition causing euvoilemic hyponatremia.\(^7,14\) Serum levels of norepinephrine and renin, which are high in hypovolemic hyponatremia and low in euvoilemic hyponatremia,\(^14\) provide better discrimination between the 2 states. If doubts persist, careful infusion of saline in relatively small volumes and monitoring of urinary water and sodium excretion and of \([Na]\), may provide useful information about the category of hyponatremia.\(^2,7,12,14\) The characterization of volume status in patients with severe hyponatremia may benefit from application of the specialized non-invasive and invasive techniques that are now available for assessment of intravascular volume in critically ill patients.\(^15\) However, we did not find any studies that investigated these techniques in hyponatremia.

The second group of hyponatremias is characterized by low serum vasopressin levels and typically low urine osmolality. Mechanisms other than vasopressin excess are primarily responsible for the water retention in this heterogeneous group, but vasopressin action may play a secondary role. This group includes hyponatremia in chronic renal failure,\(^26\) psychiatric disorders,\(^17\) potomania,\(^24\) low solute load excreted in the urine\(^19\) and the sick cell syndrome.\(^20\) Resetting of the osmostat may present with high or low urine osmolality (see below). It will be classified in this report in the category of hyponatremia secondary to high vasopressin level because patients with resetting of the osmostat have high vasopressin levels and high urine osmolality when they have hyponatremia.

**INDICATIONS AND CONTRAINDICATIONS OF VAPTANS AND DESMOPRESSIN WITH SALINE FOR EACH CATEGORY OF SEVERE HYPONATREMIA**

Several reports have analyzed the indications and contraindications of vaptan use in hyponatremia.\(^7,21-23\) Desmopressin infusion added to the infusion of hypertonic saline, the volume of which was calculated by the Adrogue–Madias formula,\(^7\) achieved the desired rise in \([Na]\) in 25 of 25 patients with severe hyponatremia.\(^24\) Overcorrection was not noted. The treatment with desmopressin infusion was provided to all the patients, regardless of the category of hyponatremia.\(^24\) Table 1 provides synoptic answers to the question whether vaptans and desmopressin are effective and safe initial treatments in each category of severe hyponatremia. The remaining text of this section provides the rationale for the statements in Table 1.

**Hyponatremias Resulting Primarily From High Vasopressin Levels**

Inhibition of vasopressin action by vaptans will cause aquaretics and increases in \([Na]\) in every category of hyponatremia. This category consists of hyponatremias occurring in endocrine disorders, including the syndrome of inappropriate vasopressin secretion (SIADH), profound hypothroidism and Addison’s disease. SIADH can develop in certain disease states or can complicate the use of certain drugs.\(^26\) Vaptans are effective in correcting hyponatremia in this syndrome\(^27\) and can be used as initial treatment. Aquaretics resulting from the use of vaptans, however, is associated with the risk of overcorrection of hyponatremia. Monitoring of \([Na]\), and urine output is imperative in this setting. Infusion of hypertonic saline is the preferred initial step in the treatment of hyponatremia with profound neurological manifestations.\(^7\) Although not dangerous, desmopressin infusion in the setting of persistently elevated urine osmolality should be considered ineffective.

The nephrogenic syndrome of inappropriate diuresis is characterized by severe hyponatremia occurring early in life,
undetectable (very low) serum vasopressin levels and urine with high osmolality. This syndrome is caused by a missense mutation in the gene of the sex-linked V2 receptor in the basolateral membrane of the principal cells of the collecting ducts. Whether there is any place for vaptans in the treatment of hyponatremia in patients with this syndrome is not known currently. Like in SIADH, desmopressin should be ineffective in this syndrome in which the high urine osmolality will not decrease during saline infusion.

Euvolemic hyponatremia is encountered in patients with severe hypothyroidism. The proper treatment for this condition is thyroid replacement, which corrects the hyponatremia. Because a vasopressin-mediated component is part of the inability to excrete water loads in this syndrome, it is expected that vaptans will be effective in correcting hyponatremia. However, information on the effectiveness of vaptans in this syndrome is lacking. Desmopressin and saline infusion may have a place in the early treatment of severe hyponatremia if thyroid hormone replacement promptly reverses the urinary diluting defect of hypothyroidism.

Secondary adrenal insufficiency is the third hormonal deficit leading to euvolemic hyponatremia. Glucocorticoids facilitate water excretion by the kidneys. Glucocorticoid deficit is associated with a vasopressin-mediated inability to excrete water loads that responds to vaptans. However, the primary treatment for this type of hyponatremia is glucocorticoid replacement. It is possible that desmopressin added to saline infusion may be useful in the treatment of severe hyponatremia if concomitant glucocorticoid administration causes an early reversal of the diluting defect. The hyponatremia of primary adrenal insufficiency with combined glucocorticoid and mineralocorticoid deficits has an important element of volume depletion. Desmopressin infusion has a role in the simultaneous correction of hyponatremia and volume defect by infusion of saline.

The concept of resetting of the osmostat has been applied to patients presenting with hyponatremia or hypernatremia who on formal testing of urinary dilution by water loading and concentration by water deprivation behave as if they have shifted their normal $[\text{Na}]$ downward or upward, respectively. The diagnosis of this syndrome requires exclusion of other types of hyponatremia. Resetting of the osmostat is usually seen in patients with chronic illness and can be combined with other mechanisms of water retention, such as low solute clearance. Measurement of urine osmolality and sodium concentration at presentation with hyponatremia should guide the choice of initial treatment. Hyponatremia resulting from resetting of the

### TABLE 1. Vaptans and desmopressin in the treatment of severe hyponatremia (effectiveness, risks, indications and contraindications).

<table>
<thead>
<tr>
<th>Category of hyponatremia</th>
<th>Vaptans</th>
<th>Desmopressin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. With high urine osmolality</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Hypovolemic | Effective | Effective
c | |
| High risk
c | Low risk | |
| Contraindicated | Highly indicated | |
| Euvolemic | Effective | Ineffective |
| High risk
c | Low risk | |
| Use with caution | Not indicated | |
| Resetting of the osmostat | Effective in some cases | Effective in some cases |
| High risk
c | Low risk | |
| Unknown usefulness | Indicated if hypovolemia is also present | |
| Hypervolemic | Effective | Ineffective |
| High risk
c | Low risk | |
| Use with caution | Not indicated | |
| **A. With typically low urine osmolality** | | |
| Chronic renal failure | Limited effectiveness | Limited effectiveness |
| Low risk | Low risk | |
| Questionable usefulness | Questionable usefulness | |
| Psychiatric disorders | Limited effectiveness | Effective |
| High risk
c | Low risk | |
| Not indicated | Indicated | |
| Beer potomania | Limited effectiveness | Effective |
| High risk
c | Low risk | |
| Not indicated | Indicated | |
| Low urinary solute load | Ineffective | Effective |
| High risk
c | Low risk | |
| Not indicated | Indicated | |
| Sick cell syndrome | Unknown effectiveness | Unknown effectiveness |
| Unknown risks | Unknown risks | |
| Unknown usefulness | Unknown usefulness | |


c Risk of worsening hypovolemia.

c Risk of overcorrection of hyponatremia.

c Effective after correction of hypovolemia and removal of the volume stimulus for vasopressin release.
Hyponatremia of Chronic Renal Failure

Hyponatremia in chronic renal failure is typically associated with hypervolemia and is often classified as hypervolemic hyponatremia. However, the mechanism of hyponatremia differs between chronic renal failure and the conditions listed in this report under hypervolemic hyponatremia. These conditions have high serum vasopressin levels and high osmolality values in the urine. The ability of the kidneys to produce urine with very low osmolality is preserved in chronic renal failure. In this syndrome, water loading leads to formation of dilute urine. In hypovolemic hyponatremia, the urine osmolality is less than 100 mOsm/kg in several subjects, whereas urine sodium concentration may be < 20 mmol/L suggesting hypovolemia, > 40 mmol/L, suggesting SIADH, reset osmostat or salt wasting and between 20 and 40 mmol/L. In this last category, a large rise in [Na+] because of a large volume of dilute urine. Desmopressin infusion is indicated, but with a note of caution. Impaired abun-
dance of aquaporin-2 protein in this syndrome may limit the effectiveness of desmopressin.

Hyponatremia in Patients With Low Urinary Solute Load

These patients present with dilute urine. However, their ability to excrete water loads is severely limited even when their urine osmolality is at the lowest attainable level. Vaptans should have no effect on water excretion when urine dilution is maximal. Solute administration, in the form of saline infusion, rapidly increases free water excretion. Desmopressin infusion, along with saline, hypertonic or isotonic, is indicated in the initial phase of treatment of severe hyponatremia in this syndrome.

Hyponatremia in Patients With Sick Cells

The concept of sick cells refers to abnormalities in the function of transport processes of the cell membranes in patients with severe illnesses, with exit of low-molecular-weight organic solutes and water into the extracellular...
compartment. The characteristic biochemical picture is one of hyponatremia, normal serum osmolality and a large osmol gap, which is the difference between measured serum osmolality and osmolality calculated as the sum of the osmotic equivalents of serum sodium, glucose and urea. The concept of sick cell as a cause of hyponatremia has been disputed. Even if this syndrome causes hyponatremia, the changes in cell volume should be opposite in the sick cell syndrome, in which cells lose water, and other hyponatremias in which cells are swollen. The role of vaptans or desmopressin in the management of this syndrome is unclear.

Figure 2 shows a flow chart of treatment of hyponatremias with a focus on the use of vaptans or desmopressin.

CONCLUSIONS

The use of vaptans for initial treatment of severe hyponatremia is associated with serious risks and is ineffective in certain categories of hyponatremia. The risks of desmopressin infusion are not significant. However, this compound will be ineffective in hyponatremia with persistently elevated urine osmolality. Cost and side effects of each treatment should also be taken into account if alternative treatments are available. Vaptans are effective in correcting hyponatremia with high levels of serum vasopressin and high urine osmolality values. They can be used as initial treatment of hyponatremias with urine osmolality that is persistently elevated but should never be used simultaneously with hypertonic saline. The risk of overcorrection of [Na], is very high in this case. Vaptans are contraindicated in hyponatremias with urine osmolality that is high initially but is lowered after saline infusion and they are ineffective in hyponatremia with dilute urine. Desmopressin infusion is ineffective for hyponatremias with persistently high urine osmolality but offers the best option for preventing overcorrection of severe hyponatremia with urine that is initially...

FIGURE 2. Initial management of severe hyponatremia.
concentrated but responds to saline infusion with dilution. Desmopressin infusion is also indicated for most categories of severe hyponatraemia with dilute urine. Characterization of the volume status is critical for the choice of treatment. Hypovolaemia in hyponatraemic patients may not be detectable by clinical means. Use of desmopressin as initial treatment of hyponatraemia if there are doubts about the presence of hypovolaemia is prudent. Monitoring of [Na]+, urine flow rate and, in selected cases, urine sodium and potassium concentration is critical during treatment of severe hyponatraemia regardless of the method of treatment. Monitoring should be intensified if vaptans are used. The use of vaptans or desmopressin in certain types of hyponatraemia will require further studies.

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