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

*Antonios H. Tzamaloukas, MD, Joseph I. 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.

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Hyponatremia is considered severe when serum sodium concentration ($[Na]_s$) is $<125$ mmol/L[1] and/or when hypertonic or isotonic saline is infused to correct severe neurological manifestations or symptomatic hypovolemia.[2] In severe cases of hyponatremia, the rate of correction of $[Na]_s$ is critical for prevention of either prolonged brain edema or osmotic demyelination.[2] The current standard is a controlled rate of rise in $[Na]_s$. Although there is some debate about how rapid the initial increase in $[Na]_s$ should be in severe hyponatremia,[3,4] there is strong evidence that the incidence of osmotic demyelination increases sharply if the correction exceeds 20 mEq/L in the first 24 hours.[5] Based on these observations, most experts recommend slower rates of correction.[3–6] Recent guidelines from an expert panel recommend a minimum rate of correction of $[Na]_s$ 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.[7] The expert panel set also upper limits in the rate of correction. $[Na]_s$ 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.[7]

Achieving the desired rate of correction of $[Na]_s$ is a difficult task. In a recent report, the rise in $[Na]_s$ in the first 24 hours of treatment exceeded 12 mEq/L in 11% of the subjects admitted with severe hyponatremia.[8] 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 $[Na]_s$ values, the concentration of sodium in the infusate and the volume of body water before the start of saline infusion.[2,9] 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 $[Na]_s$ are important sources of error in the predictive formulas.[2,10]

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.[2] Two recently proposed strategies addressed specifically the effect of urine volume and composition on $[Na]_s$ 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.[7] 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 $[Na]_s$

As we have previously discussed,[2] the changes in $[Na]_s$ can be predicted based on various clinical parameters, including initial body water volume, urine flow rate and electrolyte composition, infusate volume and composition as well as dietary

*From the Renal Section, Medicine Service, Raymond G. Murphy VA Medical Center and Department of Medicine (AHT), University of New Mexico School of Medicine, Albuquerque, New Mexico; Joan C. Edwards School of Medicine (JIS), Marshall University, Huntington, West Virginia; Division of Nephrology and Hypertension, Department of Medicine (DSR), The George Washington University, Washington, District of Columbia; Medicine Service, Raymond G. Murphy VA Medical Center and Department of Medicine (GHM), University of New Mexico School of Medicine, Albuquerque, New Mexico; Department of Surgery (RHG), University of New Mexico School of Medicine, Albuquerque, New Mexico; and Division of Nephrology, Department of Medicine (DM), University of Toledo, Toledo, Ohio.*

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*Correspondence: Deepak Malhotra, MD, PhD, University of Toledo—Health Science Campus, 3000 Arlington Avenue, Toledo, OH 43614-2598 (E-mail: deepak.malhotra@utoledo.edu).*

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

$$[Na]_{Fin} = \frac{TBW_{Ini} \times [Na]_{Ini} + 1.11 \times V_{Inf} \times [Na]_{Inf} - V_{Urine} \times \{[Na]_{Urine} + [K]_{Urine}\}}{TBW_{Ini} + V_{Inf} - V_{Urine}},$$

where $TBW_{Ini}$ is total body water before the infusion, $[Na]_{Ini}$ is the initial serum sodium concentration, 1.11 is an empiric correction term proposed by Edelman et al.[11] $V_{Inf}$ is the volume of the infusate, $[Na]_{Inf}$ is the sodium concentration in the infusate, $V_{Urine}$ is the volume of urine and $[Na]_{Urine}$ and $[K]_{Urine}$ 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 HYPONATREMIA

One large group of hyponatremias is characterized by high serum vasopressin levels and urine osmolality levels that

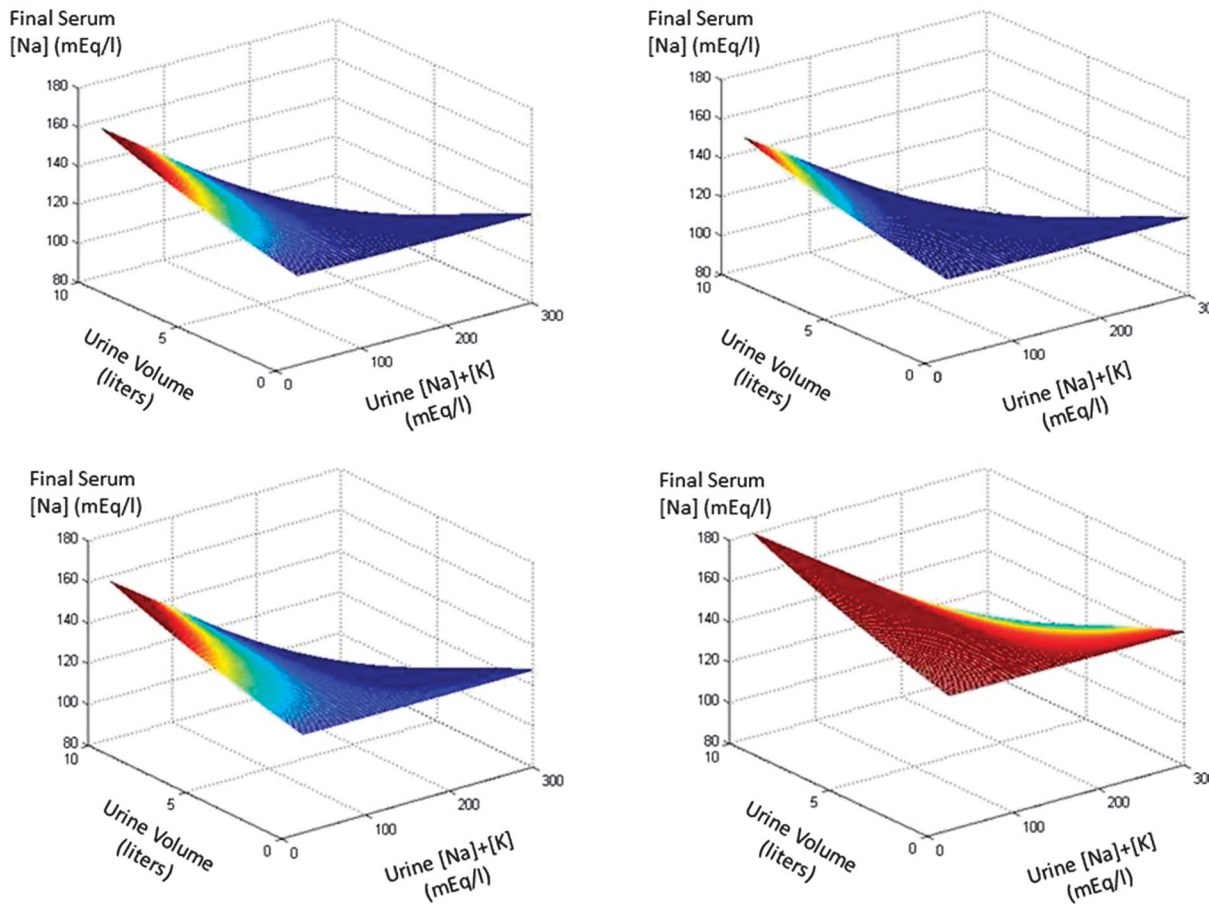


FIGURE 1. Simulations of the response of $[Na]_s$ depending on urine flow and electrolyte content as well as infusate composition and volume. We began with a 70-kg man (42 L $TBW_{Ini}$) and a $[Na]_{Ini}$ of 125 mEq/L. Simulations are shown in 4 circumstances. Top left panel: no infusate. Top right panel: 2 L of 5% dextrose in water. Bottom left panel: 2 L of 0.9% saline. Bottom right panel: 2 L of 3% saline. Urine volume and electrolyte content were allowed to range in the x and y axes between 0 and 10 L and 25 and 300 mEq/L, respectively. We present simulations as if these occurred after 24 hours and color-coded rates of correction exceeding 20 mEq/L per 24 hours as red with lesser rates of correction having hues moving toward the blue end of the color spectrum.