Treatment of Severe Hyponatremia: Conventional and Novel Aspects

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Abstract. Hyponatremia is a frequent electrolyte disorder. A hyponatremia is called acute severe (<115 mM) when the duration has been <36 to 48 h. Such patients often have advanced symptoms as a result of brain edema. Acute severe hyponatremia is a medical emergency. It should be corrected rapidly to approximately 130 mM to prevent permanent brain damage. In contrast, in chronic severe hyponatremia (>4 to 6 d), there is no brain edema and symptoms are usually mild. In such patients, a number of authors have recommended a correction rate <0.5 mM/h to approximately 130 mM to minimize the risk of cerebral myelinolysis. Sometimes it is not possible to diagnose whether a severe hyponatremia is acute or chronic. In such cases, an initial imaging procedure is helpful in deciding whether rapid or slow correction should be prescribed. The modalities of treatment of severe hyponatremia have so far consisted of infusions of hypertonic saline plus fluid restriction. In the near future, vasopressin antagonists will become available. Preliminary experience has already demonstrated their efficiency of inducing a sustained water diuresis and a correction of hyponatremia.

Hyponatremia is the most frequent electrolyte disorder in clinical medicine (1). However, physicians do not always find it easy to consider the differential diagnosis and to establish a final diagnosis. In addition, there is uncertainty regarding the best mode of treatment for hyponatremia, because both brain edema in the case of slow correction (2) and cerebral myelinolysis in the case of rapid correction (3) have been described as potential adverse outcomes for different modes of treatment. V₂ vasopressin receptor antagonists for the treatment of hyponatremia are now on the clinical horizon (4), potentially worsening the confusion.

The differential diagnosis of hyponatremia has recently been reviewed (5). This communication is therefore limited to a discussion of the issue of rapid versus slow correction of severe hyponatremia. We present a proposal to resolve problems arising in cases of hyponatremia of unknown duration. Furthermore, we discuss potentially important aspects of the novel oral vasopressin antagonists now in clinical trials (e.g., reference 4).

Acute Severe Hyponatremia and Cerebral Edema

Severe hyponatremia is arbitrarily defined by some (e.g., reference 6) as a serum sodium concentration of <115 mM; “acute” commonly indicates a duration of the hyponatremia of <36 to 48 h. A body of work by Arieff, Ayus, and coworkers (7–10) has indicated that untreated acute severe hyponatremia is associated with high rates of morbidity and death, both of which are primarily attributable to brain edema. Hyponatremia may also lead to ischemic brain damage and hypoxia resulting from noncardiogenic pulmonary edema. Commonly observed settings include acute severe hyponatremia in the postoperative state (11), particularly for premenopausal women and prepubertal children (11,12); thiazide-induced hyponatremia (13); and hyponatremia in patients with psychogenic polydipsia (14). Acute severe hyponatremia is almost always symptomatic; it causes neurologic changes ranging from drowsiness and disorientation to coma, grand mal seizures, and respiratory arrest (2). Therefore, it is recommended that such hyponatremia be rapidly corrected (15), e.g., at a rate of approximately 2.4 ± 0.5 mM/h until the range of mild hyponatremia has been reached, at which time correction should be halted for ≥24 h. Those authors used infusions of 3% saline solution to achieve a correction rate of 2.4 ± 0.5 mM/h (15). Further specifications for the optimal correction rate in selected situations, such as cases of acute severe hyponatremia involving grand mal seizures, have also been reported (8,16).

Animal experiments have facilitated analysis of the probable causes of brain edema in severe acute hyponatremia. That work demonstrated that brain cells have the ability to adapt to hypo-osmolality-induced cell swelling, as do most other cells (17). However, this process requires 48 to 72 h to reach completion (17). An initial phase of rapid extrusion of ions (Na⁺, K⁺, and Cl⁻) from the cells is followed by a slow phase, during which the intracellular concentrations of osmotically active organic osmolytes are reduced (18,19). This regulatory process serves to return the initially swollen cells to normal cell volume. During the transitional phase, i.e., before cell volume adaptation is complete, brain edema is present. Because of the rigid skull surrounding the brain, cerebral edema can lead to
decreased brain perfusion and herniation of the brainstem into the foramen magnum. These changes are preventable by rapid correction of the acute severe hyponatremia. Acute severe hyponatremia is usually a medical emergency. It causes brain edema, which is demonstrable by computed tomography (CT) or magnetic resonance imaging (MRI). It should be rapidly corrected, to prevent permanent brain damage or even worse consequences.

**Chronic Severe Hyponatremia and the Risk of Myelinolysis**

Chronic severe hyponatremia often involves mild to moderate hyponatremic symptoms. It is commonly observed in the advanced stages of the syndrome of inappropriate secretion of antidiuretic hormone, cardiac failure, and liver cirrhosis. It does not appear to cause major problems by itself. In chronic hyponatremia, brain volume regulation is intact, and there is thus no evidence of brain swelling.

According to literature reports, problems may arise when chronic hyponatremia is corrected, especially when it is corrected faster than 0.5 mM/h and when the correction process eventually reaches the normonatremic or even hypernatremic range. Norenberg et al. (20), Sterns et al. (21,22), and Brunner et al. (23) reported patients who were found to have central pontine myelinolysis or other types of cerebral myelinolysis after their chronic hyponatremia had been corrected at a rate of >0.5 mM/h. Almost all of those patients were reported from retrospective studies (20–23). Most of them had other associated risk factors for cerebral myelinolysis, such as malnutrition, hypokalemia, or liver disease. In addition, the overall incidence of the demyelinating syndrome after the correction of hyponatremia appeared to be very low (22). A recent metanalysis even reached the conclusion that, when patients with severe hyponatremia, rather than patients with established myelinolysis, were considered, the rate of correction of hyponatremia was not related to subsequent neurologic changes (23), regardless of whether the hyponatremia had been acute or chronic. However, studies using animal models also found that rapid correction of chronic hyponatremia may cause cerebral myelinolysis (24–28). Finally, it should be pointed out that correction of chronic hyponatremia is often an elective procedure, because there are no pernicious symptoms or adverse events related to that hyponatremia. Although the data are incomplete, there is more evidence favoring slow correction of chronic severe hyponatremia than favoring rapid correction.

Pontine and central pontine myelinolysis involves changes that produce the clinical signs of bulbar and pseudobulbar palsy. Imaging studies, such as CT and MRI studies, are helpful in actually demonstrating that myelinolysis has occurred (29); however, CT and MRI results become positive only 6 to 10 d after clinical signs of myelinolysis become manifest. There is no known treatment for this demyelinating syndrome. In fact, as the term “osmotic demyelination” suggests, the animal studies have been able to directly relate the myelinolysis to local osmotic imbalances that occur in the brain during rapid correction of chronic hyponatremia (24–28).

These imbalances have been attributed to slow reaccumulation of cell-protective organic osmolytes, as opposed to rapid overshooting reaccumulation of ionic osmolytes. In experimental animals, it has been demonstrated that disruption of the blood-brain barrier may occur in situations such as this, leading to myelinolysis. Because of regional differences in the brain, the pons is a preferred site for blood-brain barrier disruption and associated myelinolysis.

**Severe Hyponatremia of Unknown Duration**

In clinical practice, patients for whom the duration of severe hyponatremia is unknown are commonly observed. Such patients usually have moderate to severe symptoms, which could be related to hyponatremia or to other causes. There is no published evidence on how best to proceed in these cases. Obviously, such patients could be at risk for demyelination or for the consequences of cerebral edema, depending on the approach to treatment chosen (rapid or slow correction) and the error possibly incurred (chronic or acute hyponatremia). In our experience, it has been helpful in such cases to perform an imaging study (CT or MRI) as soon as the clinical situation permits and to plan the treatment according to the imaging results (i.e., the presence or absence of cerebral edema). However, this approach has not been studied formally; it is hoped that this will be accomplished in the future.

**Clinical Role of V₂ and V₁/₂ Vasopressin Receptor Antagonists**

The potential roles of vasopressin antagonists in the treatment of vasopressin-related disorders, such as hyponatremia, have been discussed in detail in the past two decades. It is expected that V₂ and V₁/₂ Receptor antagonists will make the treatment of hyponatremia more predictable, more “titratable,” and less burdensome to patients, in comparison with the current therapeutic approach. Current treatment usually consists primarily of fluid restriction, which is notoriously unreliable, is difficult to reinforce, and may be unacceptable to patients. In addition, studies in animal models previously demonstrated that competitive V₂ vasopressin receptor antagonists were effective in correcting the pathologic water retention in hyponatremic states. However, the agents used in previous animal studies were peptidic in nature and sometimes also had intrinsic agonistic properties; they never gained clinical acceptance (e.g., reference 30).

The situation is likely to change soon. In the past 8 yr, five different oral, competitive, V₂ or V₁/₂ vasopressin receptor antagonists have been developed to the stage of clinical testing. These new agents have been demonstrated to be effective inducers of water diuresis. Because the water diuresis occurs without a significant loss of electrolytes in the urine, the water diuresis has also been termed “aquaresis” and the agents are sometimes called “aquaretics.” Furthermore, these new substances are without significant effects on direct or indirect circulatory parameters, such as plasma renin, aldosterone, creatinine, or urea concentrations.

Do we need vasopressin antagonists? Indeed, we expect that
once such agents are widely available, they will be in demand. First, they would be helpful in the daily care of hyponatremic patients, as outlined above. Second, even in cases of chronic stable hyponatremia with no or minimal symptoms, physicians may note indications for active treatment of the hyponatremia. Such may be the case when there is a need to give the patient fluids (e.g., in the context of hyperalimentation or parenteral antibiotic treatment), when physicians become concerned that the hyponatremia may worsen, or when a patient in previously stable condition develops otherwise unexplained cerebral symptoms. Third, hyponatremia and vasopressin excess, both of which would be treatable by the appropriate vasopressin antagonist, appear to have untoward circulatory effects (31). For example, it has been pointed out that cerebral vascular V1 receptors may contribute to brain ischemia in cases of acute hyponatremic brain edema. Furthermore, Okada et al. (31) demonstrated an effect of hyponatremia per se to increase the calcium ion-activated state of vascular smooth muscle cells, thus increasing peripheral vascular resistance and sensitivity to Ca^{2+}-dependent agents such as angiotensin II in hyponatremia. To date, the latter effect has only been demonstrated in vitro. However, if it also occurs in vivo, it would help explain the presently anecdotal reports of remarkable improvement of hyponatremic cardiac failure with the administration of vasopressin receptor antagonists (P. Gross and other participating study centers, unpublished observations). Therefore, it is not unlikely that vasopressin antagonists will be agents specifically used for the treatment of hyponatremic cardiac failure.

Studies in laboratory animals have provided a body of evidence demonstrating the efficacy of vasopressin antagonists in correcting hyponatremia, ameliorating the defect in renal water excretion, and improving the overall prognosis for cardiac failure (32–36). Abraham et al. (32) recently reported on 28 patients with cardiac failure who received the oral V2 vasopressin receptor antagonist VPA 985 in a short-term study (see Table 1 for an overview of currently available vasopressin antagonists). VPA 985 decreased urinary osmolality and increased aquarexia (32). Those results were confirmed in a different study, in which VPA 985 was administered for 7 d to hyponatremic patients, including patients with cardiac failure (37). In the latter study, VPA 985 corrected the hyponatremia from an average of 127 mM to 136 mM, within 2 to 4 d, for approximately 80% of patients. For the remaining approximately 20% of patients, serum sodium concentrations were increased less; a higher dose of VPA 985 would presumably have been required for those “partial nonresponders” for correction to normonatremia, but the study protocol did not permit a dose modification. No patient became hypernatremic. Rarely (2 of a total of 112 patients), patients underwent “too fast” correction, according to the definitions of the study protocol (i.e., >10 mM/24 h). Their treatment needed to be stopped. Overall, there were no major side effects.

V2 receptor antagonists have been comparably effective in liver cirrhosis and cardiac failure; this has been demonstrated in experimental animals as well as in patients (38–40). Inoue et al. (40) administered OPC 31260, a first-generation, oral, V2 vasopressin receptor antagonist, to eight patients with biopsy-proven cirrhosis (Child-Pugh stage A or B). OPC 31260 caused hypotonic diuresis. The urinary flow rate approximately tripled. However, renal function must be monitored closely for signs of potential deterioration in cirrhosis when vasopressin antagonists are administered for longer times, as demonstrated in studies with VPA 985, a structurally dissimilar V2 receptor antagonist (38). Similarly, the hyponatremia of the syndrome of inappropriate secretion of antidiuretic hormone was treatable with V2 receptor antagonists in animal models (41,42) and in patients (38,43).

The treatment of hyponatremia will become more promising when new oral vasopressin antagonists are available. Whether such agents will also have an effect on thirst remains to be

Table 1. Properties of V2 receptor antagonists

<table>
<thead>
<tr>
<th></th>
<th>OPC 31260</th>
<th>SR 121463A</th>
<th>VPA 985</th>
<th>YM 087</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of application</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>$K_i$ in rats (nM)</td>
<td>21.7</td>
<td>1.42</td>
<td>0.48</td>
<td>3.0</td>
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<tr>
<td>$K_i$ in human subjects (nM)</td>
<td>25.4</td>
<td>4.1</td>
<td>1.12</td>
<td>1.1</td>
</tr>
<tr>
<td>Selectivity index ($V_{1a}/K_i$)</td>
<td>10</td>
<td>112</td>
<td>Not determined</td>
<td>0.1</td>
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<tr>
<td>Urine volume (DD)</td>
<td>↑</td>
<td>↑</td>
<td>↑ (DD)</td>
<td>↑ (DD)</td>
</tr>
<tr>
<td>Urine osmolality (DD)</td>
<td>↓</td>
<td>↓</td>
<td>↓ (DD)</td>
<td>↓ (DD)</td>
</tr>
<tr>
<td>Na$^+$ excretion/24 h</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>Unchanged at LD (↑ at HD)</td>
<td>Unchanged</td>
</tr>
<tr>
<td>K$^+$ excretion/24 h</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>Unchanged at LD (↑ at HD)</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Serum [Na$^+$] response</td>
<td>↑</td>
<td>↑</td>
<td>↑ (DD)</td>
<td>↑ (DD)</td>
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<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Manufacturer of agent</td>
<td>Otsuka, Japan</td>
<td>Sanofi, France</td>
<td>Wyeth-Ayerst, USA</td>
<td>Parke-Davis, USA/ Yamanouchi, Japan</td>
</tr>
</tbody>
</table>

$^a$ $K_i$, inhibition constant (concentration of antagonist required to inhibit by 50% the maximal $V_2$ effect of vasopressin); DD, dose dependent; LD, low dose; HD, high dose. Note that YM 087 is a nonspecific vasopressin receptor antagonist.
determined; to date, no such effect has been described. Work must also be performed to investigate the predictability of the correction rate for given cases of hyponatremia when vasopressin antagonists are used. No guidelines for prediction are currently available. Other questions are whether vasopressin antagonists would lower the portal pressure in cirrhosis of the liver and whether they would increase the GFR in patients with renal insufficiency. A final point concerns the role of hyponatremia in the prognosis of advanced congestive cardiac failure. It was conventionally thought that hyponatremia is an epiphenomenon related to the severity of congestive cardiac failure; however, on the basis of the potential reductions in cardiac preload and afterloads by \( V_1/2 \) receptor antagonists and the observations of Okada et al. (31), it is now conceivable that hyponatremia may contribute to the severity of congestive heart failure. In that case, vasopressin antagonists would accomplish substantially more than simply the improvement of some ce-

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