Mild Chronic Hyponatremia in the Ambulatory Setting: Significance and Management

Helbert Rondon-Berrios* and Tomas Berl†

Abstract
Mild chronic hyponatremia, as defined by a persistent (>72 hours) plasma sodium concentration between 125 and 135 mEq/L without apparent symptoms, is common in ambulatory patients and generally perceived as being inconsistent. The association between increased mortality and hyponatremia in hospitalized patients in various settings and etiologies is widely recognized. This review analyzes the significance of mild chronic hyponatremia in ambulatory subjects and its effects on mortality and morbidity. It addresses whether this disorder should even be treated and if so, which patients are likely to benefit from treatment. The available approaches to correct hyponatremia in such patients in the context of recently published panel-generated recommendations and guidelines are described.


Introduction
Numerous studies have shown a significant association between hyponatremia and mortality in patients admitted to hospitals (1,2) or intensive care units (3,4). This association is consistent and well recognized across a number of etiologies and comorbidities, including heart failure (5), cirrhosis (6), neoplasms (7), and CKD (8). Hyponatremia has been felt to be a marker of severe and advanced disease rather than a direct contributor to excess mortality (9). We reviewed whether the association observed in ill hospitalized patients extends to ambulatory patients with mild chronic hyponatremia who have mild or no symptoms. However, the accompanying brain adaptation to hyponatremia makes them prone to morbidity and treatment-related complications. We present data regarding potential outcomes of mild chronic hyponatremia and its treatment that must be weighed against the benefit afforded by its correction.

Significance of Mild Chronic Hyponatremia
Mild Chronic Hyponatremia and Risk of Mortality
As a part of the baseline evaluation of the Copenhagen Holter Study, Sajadieh et al. (10) measured plasma sodium concentration (PNa) in a cohort study aimed at addressing the value of 48-hour Holter recording in risk assessment of 671 subjects without apparent cardiovascular disease. After adjustment for age, sex, smoking, diabetes, LDL cholesterol, and systolic BP, PNa<134 and <137 mEq/L were associated with hazard ratios (HRs) for the composite end point of all-cause mortality or first myocardial infarction of 3.56 (95% confidence interval [95% CI], 1.53 to 8.28; \( P<0.05 \)) and 2.21 (95% CI, 1.29 to 3.80; \( P<0.05 \)), respectively. This association was not driven by myocardial infarction. After excluding diuretic users, even PNa in the range of 135–137 mEq/L was found to be an independent predictor of the composite end point, with an HR of 2.39 (95% CI, 1.10 to 5.18; \( P=0.03 \)).

Hoern et al. (11) measured baseline PNa in 5208 subjects in the Rotterdam Study, a prospective cohort designed to assess risk factors for various ailments in the elderly population. With a prevalence of 7.7%, hyponatremia was an independent predictor of mortality, even after adjusting for demographics and comorbidities, with an HR of 1.21 (95% CI, 1.03 to 1.43; \( P=0.02 \)).

Gankam-Kengne et al. (12) analyzed the significance of baseline PNa in the Dallas Heart Study aimed at identifying biologic, ethnic, and socioeconomic determinants of differences in cardiovascular health among 3551 subjects. The prevalence of hyponatremia was 6.3%. After adjustments for demographics, major comorbidities, and other factors, hyponatremia remained an independent risk factor for mortality, with an HR of 1.75 (95% CI, 1.08 to 2.81; \( P=0.02 \)).

In a cross-sectional study, Mohan et al. (13) measured PNa in 14,697 adults who participated in the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2004. At an estimated prevalence of 1.72%, hyponatremia was associated with an HR of death of 3.61 (95% CI, 2.31 to 5.63; \( P<0.001 \)). Following Cox regression models adjusting for demographics, comorbidities, and other factors, a highly significant association persisted.

Taken together (Table 1), the data strongly support the view that hyponatremia is associated with an increased risk of mortality in outpatients, as it is in those that are hospitalized.

Mild Chronic Hyponatremia and Risk of Morbidity
Neurocognitive Deficits. The adaptive cerebral response to hyponatremia involves the loss of osmolytes, some of which are neurotransmitters (14), making the relationship between hyponatremia and central nervous system impairment biologically plausible. Several excitatory amino acids, such as glutamate, are lost in the adaptation to cell swelling, a process known as regulatory volume decrease (15,16). It is, therefore, not
surprising that neurocognitive deficits are evident, even in apparently asymptomatic patients, when such changes are specifically probed for (17) (Table 2).

In a multifaceted landmark study, Renneboog et al. (18) performed neurocognitive testing in 16 patients with syndrome of inappropriate antidiuretic hormone secretion (SIADH), with each serving as his/her own control before and after the treatment of hyponatremia. Attention deficits were evaluated by measuring reaction times and error numbers to a series of visual and auditory stimuli presented to the patients, who reacted with a simple motor response. When hyponatremic, the mean latency and error number were statistically higher, even compared with volunteers after moderate alcohol consumption. The threshold PNa at which attention deficits significantly increased was 132 mEq/L.

In a retrospective case-control study, Gosch et al. (19) administered the Comprehensive Geriatric Assessment, a standardized tool to screen for functional and cognitive disabilities, to 129 elderly patients with hyponatremia consecutively admitted to a geriatric unit and matched them for age and sex with 129 normonatremic controls. After multivariate analysis, the patients with mild chronic hyponatremia had significantly worse outcomes in the cognitive and functional tests of the Comprehensive Geriatric Assessment compared with controls.

Gunathilake et al. (20) evaluated cognitive function in asymptomatic community-dwelling individuals from the Hunter Community Study, a population-based prospective cohort study aimed to assess factors important in elderly health. Cognitive function was higher in individuals with a PNa of 135 mEq/L compared with those with a PNa of 130 mEq/L (95% CI, 1.56 to 7.79; \( P = 0.01 \)).

**Gait Disturbances.** Another component of the study by Renneboog et al. (18) evaluated gait by measuring the total traveled way (TTW) after a 10-second tandem walk with eyes opened over a pressure-sensitive calibrated platform. TTW was significantly longer during hyponatremia compared with TTW when PNa was restored to normal (Figure 1). The TTW in the hyponatremic group was even longer than that of volunteers after moderate alcohol intake.

**Falls.** To assess the significance of gait disturbances, Renneboog et al. (18) also studied the prevalence of falls in 122 consecutive patients with hyponatremia and 244 matched controls who presented to an emergency department during a 3-year period. Hyponatremia was associated with a higher prevalence of falls (21.3%) compared with normonatremic controls (5.3%), with an unadjusted odds ratio (OR) of 9.45 (95% CI, 2.64 to 34.09; \( P < 0.001 \)). After adjusting for demographics and covariates, the OR for falls in patients with hyponatremia markedly increased (OR, 67.43; 95% CI, 7.48 to 607.42; \( P < 0.001 \)). The threshold PNa at which fall risk significantly increased was 134 mEq/L. This observation has been substantiated by later reports (Table 3).

In another small retrospective study of psychiatric patients, Bun et al. (21) investigated the association between mild chronic hyponatremia and fall risk; 91 patients with hyponatremia were matched with 157 normonatremic subjects. Using backward stepwise logistic regression, hyponatremia was associated with an increased fall risk (OR, 4.38; 95% CI, 1.33 to 14.46).

The above-described study by Gunathilake et al. (20) found not only cognitive deficits but also, after adjusting for

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**Table 1.** Studies reporting the association of mild chronic hyponatremia and mortality in ambulatory and community settings

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Cohort Size</th>
<th>Definition of Hyponatremia (mEq/L)</th>
<th>Mean PNa ± SD (mEq/L)</th>
<th>Prevalence of Hyponatremia (%)</th>
<th>Mortality Rate (%) in the Hyponatremic Group</th>
<th>Mortality Risk (Adjusted HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sajadieh et al. (10)</td>
<td>Prospective cohort</td>
<td>671</td>
<td>≤134</td>
<td>133</td>
<td>2.1</td>
<td>9.2</td>
<td>3.56 (95% CI, 1.53 to 8.28)</td>
</tr>
<tr>
<td>Hoorn et al. (11)</td>
<td>Prospective cohort</td>
<td>5208</td>
<td>&lt;136</td>
<td>133.4</td>
<td>6.7</td>
<td>2.7</td>
<td>1.21 (95% CI, 1.03 to 1.43)</td>
</tr>
<tr>
<td>Gankam-Kengne et al. (12)</td>
<td>Prospective cohort</td>
<td>3551</td>
<td>&lt;135</td>
<td>135</td>
<td>6.3</td>
<td>1.75 (95% CI, 1.08 to 2.81)</td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>14,697</td>
<td>≤132.3</td>
<td>133 (1999–2002) and 136 (2003–2004)</td>
<td>7.2</td>
<td>2.7</td>
<td>2.43 (95% CI, 2.31 to 5.63)</td>
<td></td>
</tr>
</tbody>
</table>

PNa, plasma sodium concentration; HR, hazard ratio; 95% CI, 95% confidence interval.

**Note:** Median PNa.

Composite outcome of mortality or first myocardial infarction.

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**TTW was signified over a pressure-sensitive calibrated platform.**另一个治疗组的TTW长度更长，在PNa恢复正常后（图1）。TTW在低钠血症组甚至更长，这比志愿者在适度饮酒后的情况。

**Falls.** 另一个研究成分由Renneboog et al. (18)研究的平衡通过测量在10秒的单脚站立行走时的总路程（TTW）后的眼睛睁开压力敏感的校准平台。TTW显著地更长在低钠血症情况下，与TTW被恢复到正常时的TTW比较（图1）。TTW在低钠血症组甚至更长，这比志愿者在适度饮酒后的情况。

**Gait Disturbances.** 另一个研究的成分由Renneboog et al. (18)研究的平衡通过测量在10秒的单脚站立行走时的总路程（TTW）后的眼睛睁开压力敏感的校准平台。TTW显著地更长在低钠血症情况下，与TTW被恢复到正常时的TTW比较（图1）。TTW在低钠血症组甚至更长，这比志愿者在适度饮酒后的情况。
demographics and diuretic use, that a decrease in PNa from 135 to 130 mEq/L was associated with a 32% increase in fall risk.

**Bone Fractures.** Several studies have found that hyponatremia-associated gait instability, the most likely proximate cause for the high incidence of falls, also increases fracture risk (Table 4).

Gankam Kengne et al. (22) analyzed the association between bone fractures and hyponatremia in ambulatory elderly patients. They identified 513 patients with bone fractures and matched them for age and sex with 513 controls. Hyponatremia was present in 13% of subjects in the fracture cohort but only in 3.9% of controls ($P<0.001$), with an adjusted OR for cofounders of 4.16 (95% CI, 2.2 to 4.7).

Sandhu et al. (23) studied 364 patients who presented with a large bone fracture to the emergency room over an 18-month period and matched them with 364 controls; 9.1% of patients with fracture were hyponatremic compared with 4.1% in the fracture-free control group ($P<0.01$). By regression analysis, patients with hyponatremia were 2.5 times more likely to experience a fracture ($P=0.001$).

In a secondary analysis of a retrospective study aimed at the relationship between CKD and fractures, Kinsella et al. (24) found hyponatremia in 8.7% of patients with fractures but only in 3.2% of a fracture-free cohort ($P<0.001$). This study determined the OR after adjusting not only for age and CKD stage but also, T-score, osteoporosis risk factors, and treatment. After such adjustments, the OR remained significantly elevated at 2.25 (95% CI, 1.24 to 4.09), suggesting that hyponatremia, independent of bone mineral density (BMD), is a risk factor for fractures.

In the Rotterdam Study, hyponatremia was associated with an increased incidence of nonvertebral fractures, which remained significant (HR, 1.34; 95% CI, 1.08 to 1.68; $P=0.09$), even after adjusting for age, sex, body mass index (BMI), and multiple covariates (11).

In a retrospective case-control study, Tolouian et al. (25) assessed the prevalence of hyponatremia in 249 elderly patients admitted with hip fracture and compared it with the prevalence in 44 ambulatory controls concomitantly admitted for elective hip or knee replacement surgery. The prevalence of hyponatremia in cases and controls was 16.9% and 4.6%, respectively. After controlling for age, hyponatremia was associated with an increased hip fracture risk (OR, 4.8; 95% CI, 1.06 to 21.67; $P=0.04$).

Most recently, Jamal et al. (26) studied the association of hyponatremia with fractures among 5122 elderly community-dwelling men using data from the Osteoporotic Fractures in Men Study. Baseline prevalence of hyponatremia was 1.25%. Hyponatremia conveyed a higher risk of hip fracture (HR, 3.48; 95% CI, 1.76 to 6.87) as well as a higher risk for prevalent (HR, 2.78; 95% CI, 1.46 to 5.30) and incident (HR, 3.36; 95% CI, 1.36 to 8.27) morphometric fractures (i.e., fractures identified by x-ray rather than from symptoms) compared with normonatremic subjects. After adjusting for confounders, including falls and low BMD, the relationship between hyponatremia and fractures was not reduced.

It is of interest that the above-mentioned Rotterdam Study found an association between hyponatremia and fractures independent of falls. This argues against a primary role for falls, because vertebral fractures, which were also found to be associated with hyponatremia, are usually not caused by trauma.
Verbalis et al. (27) have undertaken studies to better define the relationship between hyponatremia and bone metabolism using a rat model of SIADH. Hyponatremic rats had a reduction of bone mass of 30% compared with fluid-restricted controls that also received desmopressin but did not develop hyponatremia. There were no significant differences in serum calcium, parathyroid hormone, and urinary calcium excretion between groups. Microcomputed tomography showed a decrease in bone volume, cortical thickness, and trabecular number in all hyponatremic animals compared with controls. Hyponatremia increased the number of osteoclasts per bone area compared with controls, suggesting that increased bone resorption, rather than decreased bone formation, was the predominant mechanism.

Figure 1. | Mild chronic hyponatremia is associated with gait disturbances. The recorded projection of the center of gravity over a pressure-sensitive calibrated platform or total traveled way (TTW) in three patients (A–C) after a 10-second tandem walk from right to left with eyes opened is shown. The left panel shows the TTW during mild chronic hyponatremia, and the right panel shows the TTW after correction of hyponatremia. Irregular paths of the center of pressure were observed in the hyponatremia condition (arrows). Reprinted from reference 18, with permission.

Table 3. Studies reporting the association of mild chronic hyponatremia and falls

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Cohort Size</th>
<th>Mean PNa ±SD (mEq/L)</th>
<th>Fall Risk (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renneboog et al. (18)</td>
<td>Cross-sectional</td>
<td>366</td>
<td>126 ± 5</td>
<td>67.43 (95% CI, 7.5 to 607)</td>
</tr>
<tr>
<td>Bun et al. (21)</td>
<td>Retrospective case control</td>
<td>248</td>
<td>131.82 ± 2.99</td>
<td>4.38 (95% CI, 1.33 to 14.46)</td>
</tr>
<tr>
<td>Gunathilake et al. (20)</td>
<td>Prospective cohort</td>
<td>2550</td>
<td>135 versus 130*</td>
<td>1.32 (95% CI, 1.04 to 1.64)</td>
</tr>
</tbody>
</table>

PNa, plasma sodium concentration; OR, odds ratio; 95% CI, 95% confidence interval.

*Study compared patients with PNa of 135 versus 130 mEq/L. No mean PNa was provided.
In a follow-up study, Barsony et al. (28) examined the effects of hyponatremia on osteoclast number and activity. Exposure of murine monocytic and bone marrow monocyte culture cells taken from hyponatremic rats to low extracellular sodium concentration, while maintaining a normal extracellular osmolality by the addition of mannitol, directly stimulated osteoclastogenesis and osteoclast activity. These observations have been complemented by the work by Tamma et al. (29), which found that vasopressin receptor V1A and vasopressin receptor V2 (V2R) are present in osteoblasts and osteoclasts of wild-type mice and that vasopressin injected into these animals stimulated bone resorption by increasing osteoclast activity and inhibited bone formation by decreasing osteoblast activity through stimulation of V2R. This latter observation suggests that antidiuretic hormone (ADH) directly contributes to osteoporosis.

A cross-sectional study using the NHANES III database that investigated the association between hyponatremia in the general population ages 55 years and older and risk of osteoporosis provides the clinical significance to the above observations (27). After adjusting for age, sex, BMI, physical activity, 25(OH) vitamin D3 level, and diuretic use, hyponatremia (mean PNa was 133±0.2 mEq/L) was associated with an increased risk of osteoporosis at the femoral neck and total hip, with ORs of 2.87 (95% CI, 1.41 to 5.81; P=0.003) and 2.85 (95% CI, 1.03 to 7.86; P=0.04), respectively.

More recently, Kruse et al. (30) studied the association between hyponatremia and osteoporosis in a cross-sectional analysis of deca scans from 1575 in- and outpatients and their concurrent PNAS. Hyponatremia was associated with a lower BMD and bone mineral content at the total hip and lumbar spine in the unadjusted model but lost its significance when adjusted for sex, age, and BMI. However, using multiple regression analysis, a dose-response relationship was found between decreasing PNAS and decreasing hip BMD, bone mineral content, and T-score.

In summary, increasing data have accumulated to support the contention that mild chronic hyponatremia, while apparently asymptomatic, is associated with cognitive deficits, gait disorders, and falls. These combined with an effect of hyponatremia to promote bone loss result in an increased fracture risk (31).

Management of Mild Chronic Hyponatremia

Despite the absence of randomized control trials assessing the efficacy of various treatment approaches to mitigate the above-discussed morbidities or the increased mortality associated with hyponatremia, consensus panels in the United States and Europe have put forth expert recommendations and clinical practice guidelines, respectively, for the treatment of such patients in various settings (32,33).

We analyze herein the available approaches to treat mild chronic hyponatremia specifically for the ambulatory patient with SIADH (Figure 2). The primary goals in treating hyponatremia are to limit water intake and promote renal water excretion. The latter can be accomplished by increasing urine solute load, decreasing the medullary osmotic gradient responsible for water reabsorption, or inhibiting ADH actions (34).

Limitation of Water Intake

Because water intake in excess of the patient’s ability to excrete it is central to the pathophysiology of hyponatremia, the limitation of water intake presents a cogent option for treatment. As such, it is the most common first step taken by most physicians. Fluid restriction should include all fluids and not just water. However, what degree of fluid restriction is needed, and will this approach consistently work on every such patient? To answer these questions, it is helpful to re-examine the normal water balance, which is depicted in Table 5. Accordingly, the amount of fluid restriction required to achieve negative water balance should be less than the sum of urine and insensible losses. An alternative rule of thumb is to restrict fluid in an amount that is 500 ml less than the 24-hour urine volume (32).
A more predictable way to estimate the amount of fluid restriction that is required to achieve changes in PNa is provided by the electrolyte-free water clearance (CeH₂O) formula, which represents the amount of free water excreted by the kidneys over a 24-hour period:

\[ CeH_2O = V \times \left( 1 - \frac{UNa + UK}{PNa} \right) \]

where CeH₂O is the electrolyte-free water clearance, V is the urine volume in 24 hours, UNa is the urine sodium concentration, and UK is the urine potassium concentration.

If information about V is unavailable, ongoing CeH₂O and thereby, its effect on PNa can be assessed from a spot urine by calculating the urine to plasma electrolyte ratio \((\frac{UNa + UK}{PNa})\). A \((\frac{UNa + UK}{PNa}) > 1\) indicates a negative CeH₂O (i.e., net free water retention) and predicts a decrease in PNa. Conversely, a \((\frac{UNa + UK}{PNa}) < 1\) reflects a positive CeH₂O (i.e., net free water excretion) and predicts an increase in PNa. The recommended degree of fluid restriction that the ratio predicts is summarized in Table 6 (35).

Patients with SIADH often have \(\frac{UNa + UK}{PNa} > 1\) and therefore, a negative CeH₂O. In such cases, tolerable fluid restriction is not likely to result in improvement of PNa, and additional therapies are usually needed. Other predictors of the likely failure of fluid restriction are urine osmolality >500 mOsm/kg, 24-hour urine volume <1500 ml, and increase of PNa of >2 mEq/L in the first 24–48 hours of fluid restriction (32).

Only one randomized study performed in children with acute meningitis addressed the effectiveness of fluid restriction. Fluid restriction was effective at increasing PNa in patients with hyponatremia but did not have any advantage in improving outcomes (36). Furthermore, in data obtained in a recent registry of >3000 subjects with hyponatremia, the increase in PNa observed with fluid restriction in the first 24 hours was not significantly different from that observed in untreated patients (37). PNa usually increases slowly and only by 1–2 mEq/L with fluid restriction alone. Fluid restriction is generally poorly tolerated because of an associated increase in thirst. When fluid restriction fails or is expected to fail, other measures require consideration.

Figure 2. | Mechanism of action of drugs commonly used to treat hyponatremia. (A) ADH works by stimulating vasopressin receptors V2 (V2Rs) located in the basolateral membrane of the principal cells in the collecting duct (CD). V2Rs are \(G\) protein–coupled receptors that, when stimulated, increase cAMP production by adenylyl cyclase (ADC)-mediated conversion of ATP into cAMP. Elevated levels of cAMP activate protein kinase A (PKA), which in turn, phosphorylates stored aquaporin 2 (AQP2)-containing vesicles and targets them to the apical membrane of CD cells, increasing water permeability. The transport of NaCl into the medulla through the Na⁺-K⁺-2Cl⁻ cotransporter (NKCC2), located in the apical membrane of cells in the thick ascending limb of the loop of Henle, is essential for the generation of at least one half of the maximal medullary concentration gradient (600 mOsm/kg), which constitutes a main driving force for water reabsorption along the CD. Loop diuretics work in hyponatremia by inhibiting NKCC2 activity and therefore, interfering with the generation of a hypertonic medulla. Vaptans bind V2R, interfering with ADH action on its receptor. Demeclocycline inhibits ADC enzyme and, perhaps, also has some post-ADC actions. (B) The connecting tubule and cortical and outer medullary CD are impermeable to urea. The inner medullary CD (IMCD) is permeable to urea under the influence of ADH by activation of UTA1 and UTA3. Urea works as an osmotic diuretic in the IMCD, and, probably, along the connecting tubule and CD. In the IMCD, high luminal urea will tend to downregulate urea transporters. In addition, if luminal flow rate is high, there will be less time for urea transport. ADH, antidiuretic hormone; CIC-Kb, basolateral chloride channel; ROMK, renal outer medullary potassium channel; TALLH, thick ascending limb of the loop of Henle, UTA, urea transporters.
Promoting Renal Water Excretion
Increasing Urine Solute Load.

External Sodium Chloride. Urine solute excretion is a determinant of free water excretion (38). NaCl works in hypotremia partly by increasing urine solute load, causing an electrolyte diuresis. However, NaCl is used in conjunction with loop diuretics for treating hypotremia, where its primary role is the restoration of urinary sodium losses and prevention of negative sodium balance (39,40). No trials exist evaluating therapy with NaCl alone, and the few very reported cases using it are combined with loop diuretics. NaCl is available as 1-g (17 mEq sodium and 17 mEq chloride) tablets. Usual doses for NaCl tablets are 6–9 g daily in divided doses (e.g., 2–3 g two or three times per day).

Urea. Urea recycling and its reabsorption in the inner medullary collecting duct (IMCD) by UTA1 and UTA3 transporters play an important role in the fine tuning of renal water reabsorption (41,42). However, urea is an ineffective solute; when its rate of excretion increases (e.g., urea tablets, high-protein diet, post-ATN diuresis, or postobstructive diuresis), urea cannot be absorbed rapidly enough to equilibrate between the tubular lumen and the intracellular space of collecting duct (CD) cells. Under such circumstances, urea becomes an effective solute that obligates water excretion (43). Urea works in hypotremia by inducing osmotic diuresis and decreasing free water reabsorption in the IMCD (44) and, probably, along the connecting tubule and CD (45). In an animal model, urea improved hypotremia in SIADH by also decreasing the compensatory natriuresis that contributes to hypotremia in this syndrome (46). The only clinical evidence for the efficacy of urea in the treatment of hypotremia comes from case series (47–54). Decaux et al. (49) reported seven patients with the diagnosis of chronic SIADH who could not tolerate strict fluid restriction and were treated with oral urea 30 or 60 g/d. Despite normal water intake, urea corrected the hypotremia in all seven patients (mean PNAs pretreatment and during treatment were 115.6±6 and 136±3.5 mEq/L, respectively), with those with higher fluid intake requiring higher doses of urea (60 g/d). Although PNAs rose significantly with urea treatment, the concentrations fluctuated widely, and this variation was related to fluctuations in daily water intake. No major side effects were noted after up to 270 days of treatment. Soupart et al. (53) also reported the use of urea in a case series of 13 patients with chronic hypotremia from SIADH. PNAs increased from a mean of 125±3 to 135±3 mEq/L at 1 year with the use of vaptans. The vaptans were then discontinued, allowing for recurrence of hypotremia. Urea was then initiated for an additional 1 year, at the end of which mean PNa was again 135±2 mEq/L. Urea was well tolerated, and no major adverse events were reported. Current European guidelines favor its use as a second-line therapy (after fluid restriction) over the use of vaptans for the treatment of SIADH (35). However, there is no United States pharmacopeia formulation for urea, and it is not approved for this use by the Food and Drug Administration (FDA). Recommended doses are 30–60 g daily in divided doses (49). Urea has many advantages: it acts immediately and has minimal toxic effects, even at plasma concentrations of 193–301 mg/dl. If urine osmolality is high and renal function is well preserved, furosemide is preferred over urea, because it will take a high dose of urea to produce enough osmotic diuresis to be effective (40,55). Urea has been found to be especially effective in the treatment of the nephrogenic syndrome of inappropriate anti-diuresis, a genetic disorder caused by activating mutations in the V2R, where vaptans are ineffective (56). BUN and urine osmolality are expected to increase with urea. Urea has a bitter taste, which limits its use, but combining it with sweet-tasting substances, such as orange juice, can alleviate this problem (33,44).

Table 5. Normal water balance

<table>
<thead>
<tr>
<th>Source</th>
<th>ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingested water</td>
<td>1500</td>
</tr>
<tr>
<td>Food</td>
<td>800</td>
</tr>
<tr>
<td>Metabolica</td>
<td>300</td>
</tr>
<tr>
<td>Total</td>
<td>2600</td>
</tr>
<tr>
<td>Insensible lossesb (TEWLc and respiratory)</td>
<td>800</td>
</tr>
<tr>
<td>Total</td>
<td>2600</td>
</tr>
</tbody>
</table>

TEWLc, transdermal water loss.
abWater generated in the body by the complete oxidation of carbohydrates, fats, and proteins.
bcWater lost from the body that can be neither perceived nor measured directly.
ictTEWL is the normal, constitutive loss of water vapor from the skin in the absence of sweat gland activity.

dcThese estimates assume a urine volume of 1 L and a fluid intake closer to the maximal amount allowed by fluid restriction. UNa, urine sodium concentration; UK, urine potassium concentration; PNAs, plasma sodium concentration. Modified from reference 35, with permission.

ddPatients actually could have a negative net water loss (i.e., free water retention) if the urine to plasma ratio is significantly high.

Table 6. Recommended degrees of fluid restriction on the basis of the urine to plasma electrolyte ratio

<table>
<thead>
<tr>
<th>(UNa + UK)/PNa</th>
<th>Insensible Water Losses (ml)</th>
<th>Water Loss beyond Insensible Losses (ml)</th>
<th>Recommended Fluid Restriction (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1</td>
<td>800</td>
<td>0–800a</td>
<td>0</td>
</tr>
<tr>
<td>0.5–1</td>
<td>800</td>
<td>300–800</td>
<td>≤500</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>800</td>
<td>300–800</td>
<td>≤1000</td>
</tr>
</tbody>
</table>

aPatients actually could have a negative net water loss (i.e., free water retention) if the urine to plasma ratio is significantly high.
Decreasing Medullary Osmotic Gradient.

Loop Diuretics. The main driver for water reabsorption in the CD is the osmotic gradient generated by the renal medulla, which has toxicity of 1200 mOsm/kg at the level of the papilla. In the inner medulla, NaCl contributes to about 50% of this medullary hypertonicity, with urea contributing to the other 50%. The first step in NaCl transport to the medulla is through the Na-K-2Cl- co-transporter located in the apical membrane of the thick ascending limb of the loop of Henle cells. Loop diuretics inhibit this transporter, reducing NaCl delivered to the medulla and thereby, decreasing the medullary osmotic gradient necessary for water reabsorption in the CD and therefore, increasing free water excretion (57,58). The only clinical evidence for the efficacy of loop diuretics in the treatment of hyponatremia comes from case series, and all in combination with NaCl tablets (39,40,55,59). Of note, most of the patients in these case reports and case series improved their PNa with the combination of loop diuretics and NaCl tablets, despite a relatively normal fluid intake. Although infrequent, there have also been reports of hyponatremia in association with the use of loop diuretics (60,61). The dose of furosemide is 20–40 mg PO one time per day. Loop diuretics act immediately. They are not approved by the FDA to treat hyponatremia.

Inhibiting ADH Actions in the Kidney. Some causes of SIADH (e.g., neoplasms and idiopathic) are not readily reversible. In such cases, consideration should be given to agents that antagonize the renal action of ADH: demeclocycline or vasopressin receptor antagonists.

Demeclocycline. Demeclocycline, a tetracycline derivative, decreases the activity of adenylcyclase and consequently, cAMP synthesis (62,63) and aquaporin 2 abundance in the IMCD (63), resulting in a reversible form of nephrogenic diabetes insipidus. Case series reported modest effects of demeclocycline on improvement of PNa in patients with hyponatremia (64). However, the only clinical trial in existence is a double-blind placebo crossover study with nine psychiatric patients with episodic or chronic hyponatremia caused by primary polydipsia (65). The investigators found no significant difference in the number of episodes of hyponatremia during the period of drug administration versus the placebo period. Nonetheless, demeclocycline is used in refractory cases of hyponatremia. Appropriate dosing of demeclocycline is 600–1200 mg/d in divided doses (62). The onset of action is usually 3 to 4 days (66). Demeclocycline is not approved by the FDA to treat hyponatremia. The use of demeclocycline has been associated with serious adverse reactions, such as skin photosensitivity, risk of superinfection, and nephrotoxicity, especially in patients with cirrhosis (67). Demeclocycline nephrotoxicity seems to be dose dependent, requiring slow dose titration and monitoring of kidney function. Given concerns for serious side effects, the European clinical practice guidelines on the diagnosis and treatment of hyponatremia recommend against its use (33).

Vasopressin Receptor Antagonists (Vaptans). Vaptans directly target the mechanism of hyponatremia in high ADH states by competing with ADH for binding at the V2R in the CD. Tolvaptan is the only oral vaptan approved by the FDA for use in the ambulatory treatment of euvoletic or hypervolemic hyponatremia. The ability of vaptans to increase PNa is amply documented. In fact, vaptans are the only interventions for the treatment of hyponatremia for which there are randomized control trials (i.e., SALT1 and SALT2) (68) complemented by two well conceived meta-analyses (69,70). However, there is a risk of publication bias, because most trials on vaptans, with the exception of the SALT Trials, were done in relatively small numbers of patients, and almost all were sponsored by industry. In addition, there is almost a complete lack of head-to-head trials comparing vaptans with other used therapies. To avoid overcorrection, vaptans must be initiated and reinitiated as inpatient with frequent PNa monitoring. Tolvaptan is started at a dose of 15 mg daily. It may be increased to 30 mg after 24 hours and then, 60 mg after another 24 hours. To mitigate the rate of PNa increase, patients should not be fluid restricted for the first 24 hours. Long-term administration for up to 4 years suggests maintenance of effectiveness (71).

Several limitations must be considered in the use of vaptans. As is also the case with urea and demeclocycline, vaptans are contraindicated in hypovolemic hyponatremia and are not indicated in patients with severe neurologic symptoms, such as seizures, because they have not been tested in such subjects and the onset of changes in PNa is not rapid enough (at least 4–8 hours) to promptly address the symptoms. Vaptans are metabolized by CYP3A4, and therefore, caution should be exercised when coadministered with CYP3A4 inhibitors (e.g., ketoconazole) or inducers (e.g., rifampin), which increase or decrease drug levels, respectively. More recently, concerns regarding liver toxicity have emerged. The TEMPO 3:4 Study designed to determine the efficacy and safety of tolvaptan in the treatment of autosomal dominant polycystic kidney disease (72) reported an increase in liver function tests in the tolvaptan group compared with the placebo group. It is worth mentioning that the dose of tolvaptan used in this study was four times the dose used in the hyponatremia trials, in which no such toxicity was observed. The FDA recommends against using tolvaptan in patients with liver disease or for a period >30 days.

The development of osmotic demyelination syndrome (ODS) is always a concern when hyponatremia is corrected. Although PNa reached the hypernatremic range in some patients involved in the mentioned trials, ODS was not reported in any of them. Since then, in total, 12 patients with ODS in association with tolvaptan have been reported. Only two of those cases have been published (S.A.A. Harb and C. Alraies, unpublished data) (73). However, some other factors could have contributed to PNa overcorrection in the published cases. In the first case, tolvaptan was continued for 4 days, despite an initial increase of PNa from 126 to 142 mEq/L, with further overcorrection to 181 mEq/L by day 4 when tolvaptan was finally stopped. In the second case, the use of tolvaptan was in close temporal relationship with hypertonic saline use. The other 10 unpublished cases have been reported to the FDA (74). These adverse events generated a letter of warning from the producing company (75). A failure to respond to vaptans may occur in some settings (76). These include the presence of very high circulating ADH levels, a vasopressin-independent diluting defect (low distal delivery as a consequence of decreased GFR and enhanced proximal tubular reabsorption as in advanced heart failure or cirrhosis), excessive water intake, and the nephrogenic syndrome of inappropriate antidiuresis (56).
Notwithstanding the well established effects to increase PNA, there are no data to ascertain whether vaptans affect the above-described mortality or alter the risk for various morbidities associated with hyponatremia. Likewise, there is uncertainty as to whether vaptans decrease health resources use by affecting hospitalization rates and length of stay. There was a statistically insignificant trend in this direction in an analysis of the EVEREST Trial (77) and a significant effect in the SIADH subgroup in a post hoc analysis of the SALT Trials (78). However, for the average patient, the cost of vaptans remains an impediment for their use (79). The lack of mortality and morbidity benefit coupled with concerns about efficacy and safety led the European practice guidelines committee to not recommend the use of vaptans in euvolemic hyponatremia and even recommend against its use in hypervolemic hyponatremia (33). This is in stark contrast to the recommendations of an expert panel that views the use of vaptans as a reasonable option in both settings (32). It should be noted that the latter panel was supported by funding from Otsuka America Pharmaceuticals Inc., the manufacturer of tolvaptan, and that a substantial proportion of the panel members also had funding from Otsuka America Pharmaceuticals Inc.

Conclusions

Mild chronic hyponatremia is not benign as previously thought and can directly contribute to increased morbidity and possibly, mortality (31,80). Although some of the above pathology is clearly related to hyponatremia, whether treating and the disorder will reverse this sequence of events is not yet known. We are of the opinion that patients with mild chronic hyponatremia associated with unstable gait, recurrent unexplained falls, a high fracture risk, or severe osteoporosis might benefit from treatment. The benefits versus risks probably shift in favor of the long-term ambulatory use of tolvaptan when fluid restriction and all other therapies have failed. We recommend that future studies address the following issues: (1) the efficacy, safety, and tolerability of urea in the treatment of hyponatremia; (2) the efficacy and safety of vaptans compared with other therapies; and (3) the effects of vaptan and other therapies on meaningful patient outcomes, such as falls and fractures.

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