Reconsidering Chronic Hyponatremia in Psychosis

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The introduction of vasopressin-receptor antagonists (vaptans), along with new information regarding morbidity and mortality, has stimulated a reconsideration of the importance of chronic hyponatremia in psychotic patients.[1] Hyponatremia (serum sodium concentration < 136 mEq/L) is the most common electrolyte disorder seen in psychotic patients, with prevalence rates ranging from 7%–10% among inpatients.[2,3]

The presence of hyponatremia seldom evokes much concern among mental health professionals unless an acute drop in serum sodium level leads to frank neurologic symptoms.[1,4,5] Acute hyponatremia can cause cerebral edema resulting in confusion, stupor, coma, and seizures.[6] Left untreated, acute hyponatremia can lead to irreversible neurologic damage, respiratory arrest, and even death. The symptoms often progress with little warning and constitute a medical emergency. Complicating the situation is the risk of correcting acute hyponatremia too quickly, which can cause severe damage to the myelin sheath of neurons in deep brain structures,[7,8] a condition known as osmotic demyelination syndrome (ODS). Fortunately, acute hyponatremia is relatively rare among psychotic individuals.

More common is mild-to-moderate chronic hyponatremia (CHN) that develops slowly over days (> 2 days) or even weeks. The slow onset allows adaptive mechanisms to reduce brain cell volume and limits cerebral swelling. The spectrum of symptoms is usually vague and includes fatigue, disorientation, headache, weakness, irritability, lethargy, confusion, and even hallucinations, all of which are difficult to distinguish from symptoms of psychosis itself.[1] Until recently, the few available treatment options have been suboptimal and seldom used.[8] As a result, CHN is generally considered benign, asymptomatic, and a harmless complication of an underlying disease or treatment side effect and often goes unrecognized and/or unmanaged.[9]

Understanding the Risk of Chronic Hyponatremia in Psychosis

Recent evidence indicates that CHN is a significant health problem leading to subtle but life-changing consequences. These include increased risk for falls,[10] attention deficits,[10] osteoporosis and fractures,[11,12] and increased mortality for inpatients[13] and outpatients.[14] In animal studies, CHN has been shown to cause increased bone resorption and reduced bone mineral density, as well as the development of hypogonadism, skeletal muscle sarcopenia, and cardiomyopathy,[15] suggesting adverse consequences across multiple organ systems with long-term health implications.

In humans, the landmark study of Renneboog et al[10] found that elderly patients with supposedly "asymptomatic" CHN presented with falls approximately 4 times more often than controls (21% vs 5%), in addition to having gait and balance problems and slow reaction times that mimicked the symptoms of excess alcohol consumption. Importantly, the study also showed that these symptoms were corrected when serum sodium level was normalized.

Comparable evidence is beginning to appear within the psychiatric literature. Bun et al[16] recently reported that, among psychiatric inpatients, 12.09% (11/91) of the hyponatremia cases had a history of falls, compared to 2.55% (4/157) of the controls. Our group[17] found that treating CHN in psychotic inpatients reduced the number of falls and overall resource utilization. Psychiatric inpatients with CHN require emergency transfer to a general hospital twice as often (26.7% vs 13.1%) as normonatremic inpatients.[18] A 20-year mortality study[19] found that life expectancy of psychotic patients with polydipsia and CHN is shortened by a decade. These mortality findings align with a much larger prospective study[20] (N = 98,411 adult medical patients) showing that patients with CHN had an increased risk of death in the hospital, at 1 year, and at 5 years. These findings have obvious implications for quality of life and raise numerous questions. When does CHN become symptomatic in psychotic populations? Is the CNS of psychotic individuals unusually vulnerable to the consequences of CHN? When should CHN be treated with medications? What dosage and duration are appropriate?

A New Treatment Option

Vaptans have generated great expectation as a treatment option for CHN.[21] One US Food and Drug Administration (FDA)–approved vaptan, tolvaptan, is a selective vasopressin (V_2) receptor antagonist.[22] It works by blocking the effects of the pituitary hormone arginine vasopressin (AVP) on the V_2 receptors on the renal collecting duct cells. The Study of Ascending Levels of Tolvaptan (SALT) trial established short-term (30 days) efficacy of tolvaptan for elevating and maintaining serum sodium levels among patients with CHN of diverse etiologies. The SALT trial included a subgroup of psychotic patients with idiopathic CHN and demonstrated that short-term treatment with tolvaptan is effective and safe in this population as well.[23] A multiyear study with psychotic patients confirmed that tolvaptan is effective and safe over long periods of time.[24] Another oral vaptan, lixivaptan, is effective and safe when used to treat CHN in psychotic patients[25,26] but is not yet FDA-approved.

Vaptans are seldom used in psychiatric institutions. The available information regarding vaptans and psychosis comes almost entirely from pharmaceutical industry–sponsored clinical trials, and, as a result, little "real-world" experience has been reported. The metric used to demonstrate vaptan efficacy has been serum sodium levels, which are thought to be of limited clinical value within the mental health context. There are no specific guidelines regarding treatment of CHN in psychotic populations, which means that clinicians need to rely solely on their clinical experience and good judgment on a case-by-case basis. Finally, the cost of tolvaptan ($250 per tablet) has raised significant cost-benefit considerations.

Meeting the Therapeutic Challenge

Given this background, we believe that certain diagnostic and therapeutic principles for treating psychotic patients with CHN can now be articulated.

To begin, it is crucial to recognize the great individual variability in the level of serum sodium at which neurologic symptoms can appear. Some patients with serum sodium levels of 120 mEq/L or less can be alert and without overt neurologic symptoms, while other patients with the same or higher serum sodium levels might be comatose, stuporous, or seizing. Thus, the immediate clinical response to CHN depends primarily on neurologic symptom severity. Fortunately, the vast majority of psychotic patients with CHN *do not* require urgent treatment.

Most psychotic patients exhibit CHN of unknown duration with nonspecific symptoms that can be easily missed by standard clinical examination.[1,6] When CHN is actually diagnosed, the underlying cause can sometimes be successfully treated. Common factors that increase the risk for CHN should be evaluated, including recent surgery or injury, very young or old age, renal dysfunction, adrenal insufficiency, hypothyroidism, cirrhosis, congestive heart failure, and various CNS disorders. However, in most cases, the underlying etiology of CHN in psychosis is unclear—it has even been suggested that psychosis with impaired water excretion represents a bona fide subtype of the psychotic illness.[27,28]

Psychopharmacologic medications increase risk of CHN. This was initially observed in patients receiving typical antipsychotic agents, tricyclic antidepressants, or a combination of both and has also been observed in patients receiving atypical antipsychotics, selective serotonin reuptake inhibitors, and anticonvulsants, among others (see review[1]). The mechanisms by which these drugs produce CHN are poorly understood. Adding ambiguity are drug side effects such as orthostatic hypotension, nausea, or vomiting, which are known to stimulate inappropriate secretion of AVP. Some psychotropic drugs themselves, such as nicotine, phenothiazines, and tricyclics, directly stimulate the release of AVP or enhance renal sensitivity to AVP. Others, such as desmopressin, oxytocin, and ecstasy, have direct renal effects and/or potentiation of AVP effects (for review, see Verbalis et al[8]). In some cases, dose reduction or switching medication can be effective, but at present clinicians have only their good judgment to guide them. The clinical stability of a patient may preclude medication modification, and drug interactions should be carefully considered.

Case-specific clinical and laboratory findings may reveal predisposing conditions and suggest a management plan. Some patients require active management, whereas others recover without intervention. Fluid restriction is still the treatment of choice, but it is often undermined by poor compliance in psychotic populations. Treatments with oral sodium chloride tablets and electrolyte-containing beverages have been suggested[8]; however, sodium supplementation is usually suboptimal, because the essential pathophysiology is water retention rather than salt depletion. When fluid restriction or sodium supplementation fails to normalize serum sodium level, clinicians occasionally turn to off-label treatments (eg, urea, loop diuretics, demeclocycline), with limited success.[8] It is in these circumstances that a vaptan should be considered as a therapeutic option.

Vaptan therapy is effective and well tolerated in psychotic patients, but drugs in this class are potent aquaretics requiring close vigilance of the trend in a patient's serum sodium levels. Discontinuation of vaptans usually results in a rapid decrease in serum sodium to baseline levels.[22–24] This suggests that the predisposing factor(s) for CHN in most of these cases is chronic, requiring long-term maintenance therapy—and maintenance treatment raises significant cost-benefit issues. Fortunately, tolvaptan is made available by the manufacturer through a patient assistance program,[29] although to date it has not been widely utilized for psychotic patients.

Conclusion

Why is hyponatremia clinically relevant for psychotic patients? In the past, the more obvious answers were because of cerebral edema and the risk of ODS. These neurologic conditions represent the 2 most severe complications of hyponatremia, and most mental health professionals have learned to recognize and deal with these extreme situations.

It is not these extreme cases, but the much larger group of psychotic patients with mild-to-moderate CHN and subtle neurologic symptoms who may receive insufficient diagnostic evaluation and inappropriate management. The Renneboog study[10] should change our concept of chronic "asymptomatic" hyponatremia. CHN can no longer be accepted uncritically as "nothing but" a harmless complication of an underlying disease or treatment. The possibility that subtle but important neurologic symptoms can be avoided warrants serious consideration.[30] The potential to prevent or at least minimize falls and fractures could have a significant impact on morbidity and mortality in psychotic populations.

Fortunately, the availability of the vaptans has opened up the potential for effective and safe treatment, particularly if fluid restriction fails to be effective. Hopefully, this new class of drugs will stimulate clinical investigation into an unmet medical need of a significant proportion of patients with psychosis.

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Addendum: As this article was going to press, the authors were notified that 3 patients enrolled in a 3-year tolvaptan study and its extension trial of about 1,400 patients with autosomal dominant polycystic kidney disease (ADPKD) developed significant (> 3 × ULN) increases in serum alanine aminotransferase with concomitant, clinically significant (> 2 × ULN) increases in serum total bilirubin. Two of these cases were previously reported in the publication of the placebo-controlled study in ADPKD.[1] These patients were treated with doses between 60 and 120 mg/d. The maximum FDA-approved dose of tolvaptan in the US for the indication of euvolemic and hypervolemic hyponatremia is 60 mg/d. Tolvaptan is not currently approved for the treatment of ADPKD. Also, in published results from populations with other diseases treated with tolvaptan over multiple years, liver enzyme abnormalities have not been observed more commonly than with placebo. However, the risk of potentially serious or life-threatening liver damage with tolvaptan cannot be excluded. An update on this important safety warning is on MedWatch: http://www.fda.gov/safety/medwatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm336669.htm.

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