Treatment of Hyponatremia

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Abstract

Hyponatremia is an electrolyte disorder that is defined by a serum sodium concentration of less than 136 mmol/L. Hyponatremia occurs at a high incidence. It is commonly associated with mild to moderate mental impairment. Hypoosmolar hyponatremia occurs in the setting of plasma volume deficiency (“hypovolemia”, e.g. after gastrointestinal fluid loss), liver cirrhosis and cardiac failure (“hypervolemic” hyponatremia) and syndrome of inappropriate antidiuretic hormone secretion (“euvolemic” hyponatremia). Excessive antidiuretic hormone and continued fluid intake are the pathogenetic causes of these hyponatremias. Whereas hypoosmolar hyponatremia is best corrected by isotonic saline, conventional proposals for euvolemic and hypervolemic hyponatremia consist of the following: fluid restriction, lithium carbonate, demeclocycline, urea and loop diuretic. None of these nonspecific treatments is entirely satisfactory. Recently a new class of pharmacological agents—orally available vasopressin antagonists, collectively called vaptans—have been described. A number of clinical trials using vaptans have been performed already. They showed vaptans to be effective, specific and safe in the treatment of euvolemic and hypervolemic hyponatremia.

Key words: hyponatremia, vasopressin receptor antagonist

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Introduction

Hyponatremia is defined by a serum sodium concentration of less than 136 mmol/L (1). It is the most frequent electrolyte disorder of patients in the hospital (2) but it is also encountered in ambulatory outpatients especially in the elderly (3). The incidence of hyponatremia has apparently increased over the last 3 decades. Although a prospective study from 1985 reported an incidence of 2.5% from a tertiary care medical center (4), more recent studies from 2003 (5) and 2006 (2) found this number to be between 29 and 42%. Although hyponatremia in the hospital was not limited to special fields of medical practice, the departments of internal medicine, surgery and gynaecology and the areas of intensive care, pulmonology and cardiology were those most heavily involved (2).

Clinical Relevance of Hyponatremia

Until recently the clinical relevance of hyponatremia, especially in its mild form (130-134 mmol/L) was not clarified. Clinicians saw hyponatremia primarily as an important diagnostic marker which indicated the presence of heart failure, liver cirrhosis or neoplastic disease. Clinicians were also well aware that acute severe hyponatremia (a serum sodium concentration <118 mmol/L of a duration <36-48 hours) would lead to serious symptoms such as confusion, unconsciousness, grand mal seizures and even death. Hence, it was common to direct therapy at the prevention of progression from mild to severe hyponatremia. However mild hyponatremia in itself—which is by far the commonest form of hyponatremia encountered—was considered oligosymptomatic, exerting little if any impairment of the patient’s wellbeing. There have been several recent changes regarding the viewpoint of these aspects.

There is new evidence that even mild hyponatremia is a cause of important symptoms (3). Renneboog et al (3) evaluated mental functions in 16 elderly individuals (age 63 ± 15 years) with chronic hyponatremia (126 ± 5 mmol/L) due to the syndrome of inappropriate ADH secretion (SIADH). The researchers performed tests of balance, directed walking, memory, calculation and speed of reactions. Importantly the researchers did one set of tests while the in-
Individuals were in hyponatremia and they performed the same set of tests at another time in normonatremia. It was found that hyponatremia caused: 1) the patients’ balance and gait to be unsteady—predisposing them to falls—, 2) made reaction time significantly longer, and 3) made mental errors significantly more common than was seen in normonatremia. In additional tests in normal healthy individuals the authors quantified the degree of mental impairment by comparison with the results of drinking alcohol. They found that a blood alcohol level of 0.6 ± 0.2 g/L led to the degree of mental impairment that had been observed previously at a serum sodium concentration of approximately 126 mmol/L. In another part of the study of Renneboog and colleagues (3), the authors analyzed more specifically the physical consequences of the dysbalance in hyponatremic patients. They studied emergency—room admissions for the incidence of preceding falls. They found that hyponatremic patients had fallen approximately four times more often than their matched normonatremic counterparts in the very recent past. Hence, it is most likely that hyponatremia predisposes to bone fractures. Taken together, even mild chronic hyponatremia is a cause of important symptoms.

Furthermore there has been continued interest in the prognostic significance of a given hyponatremia. Heumann et al studied 507 cirrhotic patients on the waiting list for liver transplantation (6). In this cohort of obviously very sick patients hyponatremia turned out to be an independent predictor of survival or premature demise—even when the score of severity—the MELD score—was average and not extreme (6). In a similar line, hyponatremia at the time of liver transplantation was associated with a larger intensity of neurologic disease, renal failure, infectious complications and early posttransplantation demise than normonatremia (7). These recent publications therefore reinforce previous knowledge depicting hyponatremia as a marker of a guarded prognosis; yet they leave the second question unanswered: does it actively contribute to an adverse prognosis?

In chronic cardiac disease hyponatremia is frequently seen. As has been well described several years ago hyponatremia in that setting predicts worsening of the heart failure and an unfavourable prognosis (8). It has now been shown that hyponatremia is also a common finding in acute ST-elevation myocardial infarction (9). A recent study of 978 acute ST-elevation myocardial infarction patients showed that hyponatremia predicted post discharge re-hospitalization and post discharge demise (9). It is noteworthy that these patients did not show cardiac failure at the time of the myocardial infarction. Again the data confirm previous knowledge of hyponatremia as a marker of an adverse prognosis; they do not answer the question whether hyponatremia in itself—or by means of the stimulated vasopressin—contributes to the worsening of the prognosis. However, recently studies using novel vasopressin antagonists have been initiated to test this latter hypothesis (10).

Pathophysiology of Hyponatremia

Precise measurements of the serum sodium concentration became available in 1950 with the introduction of flame photometry into laboratory medicine. Shortly thereafter it was suggested that excessive antidiuretic hormone (ADH, vasopressin) was responsible for most cases of hyponatremia (11). Leaf and Mamby gave a standard oral water load to hyponatremic patients (11). The serum sodium concentration fell and the urinary flow rate as well as urinary osmolality remained unchanged. A bioassay for the measurement of ADH was done and it indicated elevated ADH already at baseline before the water load. Such a pattern of changes was reminiscent of that observed when a standard oral water load was given to normal healthy volunteers having received an injection of vasopressin shortly before (12). In laboratory animals hypotonic infusions together with i.v. vasopressin were also shown to bring about hyponatremia (13) whereas either component alone was not effective. As a mirror image of the foregoing: when hypophysectomized dogs (14) or vasopressin deficient Brattleboro rats (15) were subjected to manoeuvres—such as right heart failure or liver cirrhosis—that ordinarily elicit water retention and hyponatremia, this was no longer observable.

The introduction of the radioimmunoassay for ADH in 1973 permitted a more rigorous testing of the previous concepts. Measurements of ADH have now been made in experimental hyponatremic cirrhosis (15), cardiac failure (16), glucocorticoid deficiency (17) and several other hyponatremic conditions. It was confirmed in all that the hyponatremic state was associated with stimulated vasopressin, i.e. measurable vasopressin—since osmotically it should be fully suppressed and unmeasurable in hypoosmolality. Similar findings have also been reported from patients with hyponatremia in the conditions of cardiac failure (18), liver cirrhosis (19), hypothyroidism (20), and SIADH and other settings. Uniformly all these studies found ADH to be measurable, i.e. stimulated and not suppressed.

A surprising feature of the experimental and clinical reports is the fact that ADH was secreted despite the presence of hyponatremia, synonymous with hypoosmolality. It was therefore proposed that other stimuli of ADH called “nonosmotic” would be in operation in hyponatremia. It was later found in many or most settings of hyponatremia that the non-osmotic stimuli could be traced back to baroreceptor function in large arterial vessels of the central circulation (21). For instance in hyponatremic cardiac failure baroreceptor afferents from the central arteries and the aortic arch sense the low cardiac output and transmit a vasopressin stimulating signal to the hypothalamus/baroreceptor denervation prevents such vasopressin stimulation (16). A similar chain of events is in operation in hyponatremic liver cirrhosis or extracellular volume depletion. In SIADH paraneoplastic secretion of ADH or direct involvement of the hypothalamus by cerebral changes usually explains the nonosmotic ADH.
Clinical Settings of Hyponatremia

For the diagnosis and treatment of a given hyponatremia the clinical evaluation has to include a careful medical history, a physical examination with attention to the patient’s extracellular fluid volume status and laboratory measurements. The latter should include the plasma-osmolality, potassium, -uric acid, -urea and-glucose. The urinary osmolality and the urinary sodium concentration are also required.

Hyponatremia in the presence of hyperosmolality is usually due to hyperglycemia or occasionally to mannitol causing a shift of water from the intracellular to the extracellular compartment—because the cell membrane is impermeable to the glucose in uncontrolled diabetes or the mannitol. This hyponatremia is a disorder of water distribution and not one of water balance. Hence treatment should be directed towards hyperglycemia and its correction with insulin in the case of hyperglycemic hyponatremia, but not towards ADH or water. Hypoosmolar hyponatremia may occur in the presence of advanced renal failure (stages IV or V of renal failure). It is then primarily due to the kidney’s inability to filter and excrete enough water. This hyponatremia also is not a disturbance of ADH.

The remaining entities of hypoosmolar hyponatremia— and the ones to be discussed herein—will be those that are associated with cardiac failure and liver cirrhosis (also called “hypervolemic” hyponatremia because of edema formation), SIADH (also called “euvolemic” hyponatremia) and “hypovolemia” (as occurs after gastrointestinal fluid losses or profuse sweating). SIADH is associated with a unique pattern of laboratory abnormalities: low or even subnormal serum-urea, -creatinine and importantly-uric acid, whereas the sodium excretion rate will be high (>40 mmol/L). In the hypervolemic and hypovolemic hyponatremias the laboratory measurements are changed in the opposite direction from the ones just mentioned. The urinary osmolality will be higher than 100 mosm/kg in all conditions. This indicates the kidney’s inability to excrete maximally dilute urine, one which would correct any hyponatremia.

Conventional Treatment of Hyponatremia

In the entity of hypovolemic hyponatremia infusions of isotonic saline are the treatment of choice. Such infusions will saturate the baroreceptors, terminate the stimuli to ADH secretion and allow the kidneys to excrete excess water, i.e. correct any hyponatremia. In euvolemic and hypervolemic hyponatremia saline infusions may occasionally be given as an emergency measure—i.e. in grand mal seizures or in very severe hyponatremia (<110 mmol/L) with major mental changes—but in general this approach is unproductive. Instead other measures focusing on reducing total body water have been recommended in the literature:

A standard procedure is the prescription of a fluid restriction to approximately 0.8 L/day. Given that obligatory urinary excretion plus insensible losses yield > 1 L/day of fluid volume, this kind of a fluid restriction should result in a negative fluid balance and hence an increase in the serum sodium. However the improvement will occur at a slow pace. Furthermore hyponatremic patients are thirsty patients—if they were not they would stop drinking and they would not become hyponatremic in the first place. It is therefore notoriously difficult for hyponatremic patients to adhere to a fluid restriction (1) and this measure may not work.

The use of pharmacologic agents has been suggested for the induction of a nephrogenic diabetes insipidus. This can be expected to correct a hyponatremia (22, 23). Thus, lithium in lithium carbonate is an inhibitor of ADH induced adenylate cyclase in the collecting duct principal cell. Hence, lithium antagonizes the hydroosmotic effect of ADH (22). However lithium is potentially nephrotoxic, its plasma levels vary and have to be watched closely (24) and the effects on renal water excretion are not reliable.

Demeclocycline is an older tetracycline antibiotic. One of its adverse effects was polyuria and nephrogenic diabetes insipidus. Doses of 600-1,200 mg/day have been given to treat hyponatremia (23). Although demeclocycline is more effective and more predictable than lithium in the treatment of hyponatremia (23) demeclocycline may induce azotemia in general and it may be nephrotoxic in liver cirrhosis (25). Furthermore demeclocycline is no longer available on the market in most countries.

Urea given as a powder or in the form of capsules in doses of several gram/day has been used. It induces an osmotic diuresis and an augmented excretion of free water by the kidneys. This has been used successfully by some to correct the hyponatremia of SIADH (26); however urea has not met with widespread acceptance by patients and physicians.

In SIADH high doses of i.v. loop diuretics elicit a voluminous diuresis that has a low sodium content. If the sodium excreted is replenished quantitatively by giving hypertonic saline, a negative water balance ensues and hyponatremia can be corrected in this way (27). This treatment is effective and reliable, but it is cumbersome. Therefore it is not used very frequently. Taken together, the conventional approaches for the treatment of hyponatremia lack specificity, efficiency and ease of application. Therefore scientists have been interested in other means such as vasopressin antagonists to improve the treatment of hyponatremia.

Vasopressin Antagonists

The pathogenetic role of ADH in most types of hyponatremia suggested that vasopressin antagonists would be a suitable approach to treatment. Manning et al were the first to describe a large number of peptidic vasopressin antagonists (28). It was shown that antagonists worked in principle in animal models with hyponatremia and in human subjects (29). However the peptidic nature of the agents, the need for
parenteral application and the unexpected property of intrinsic agonistic effects in addition to antagonistic effects precluded any widespread or chronic use in patients. It was therefore a breakthrough that random screening between 1990 and 2000 yielded several non-peptide, orally available novel vasopressin antagonists collectively called vaptans (Fig. 1).

Mozavaptan

OPC 31260 or mozavaptan was described in 1992 (30). It is a benzazepine derivative (Fig. 1) that bound with a high degree of affinity to the renal hydroosmotic V-2 vasopressin receptor but not to the vascular V-1 vasopressin receptor. It did not cause agonistic effects of its own. When given orally to normal human subjects at a dose of 1 mg/kg the urinary flow rate increased eight fold, the urinary osmolality became maximally dilute (63 mosm/kg) but the urinary sodium excretion rate changed only marginally (31). Although mozavaptan was the first agent of the new class of vaptans and hence had paradigmatic importance mozavaptan was not very potent. Mozavaptan eventually met with limited clinical application and subsequent agents have attracted greater interest.

Lixivaptan

VPA 985 or lixivaptan is a potent, V-2 receptor selective, orally available vasopressin antagonist reported in 1998 (32). Recently, a short term study in 42 heart failure patients receiving lixivaptan was reported (33). When lixivaptan was given in doses as high as 400 mg the urinary excretion rate more than doubled, solute-free water excretion was significantly enhanced and the serum sodium concentration increased (33). A prospective randomized study in 112 patients with euvolemic and hypervolemic hyponatremia was also performed. The study extended over 7 days. Patients were placed on a fluid restriction of 1 L/day. They received 50 or 100 mg of lixivaptan twice a day per os.

In the placebo control group the serum sodium remained unchanged (127.3 ± 3 mmol/L at baseline, 127.7 ± 4 at the end of the study) however, there was a significant increase in the high dose lixivaptan group (receiving 200 mg of lixivaptan/day): the serum sodium went from a baseline of 126.4 ± 4.4 mmol/L to 132.3 ± 6.9 at the end of the study (p <0.05). The increase of the serum sodium occurred within two to three days after the start of lixivaptan treatment. Patients with a diagnosis of SIADH responded better than those with liver cirrhosis or cardiac failure. In fact only 55 % of hyponatremic patients with liver cirrhosis responded with an increase of the serum sodium. The causes for the apparent unresponsiveness in this many patients have not been clarified. However, it is likely that decreased distal delivery of tubular fluid to the collecting duct is involved. The lixivaptan treatment was associated with a slight, 8% decline of the GFR (34). The excretion rates of sodium and potassium remained unchanged. There were very few side effects. Primarily patients noted an increase in thirst. There were no specific serious adverse events.

Conivaptan

Conivaptan or YM 087 is the first combined V-1a/V-2 vasopressin receptor antagonist (35). A few clinical studies have been reported using conivaptan as a parenteral preparation (36). [Although originally developed as an oral antagonist it was later marketed as a parenteral agent only]. The studies included patients with SIADH and hyponatremic cardiac failure. Conivaptan was given as a continuous i.v. infusion over 9 days in doses of 40-80 mg/day. Patients were supposed to be on a mild fluid restriction of 2 L/day. Conivaptan increased the urinary flow rate significantly, diluted the urine, caused a positive free water balance and increased the serum sodium concentration from 125 ± 33 mmol/L to 133 ± 3.7(p <0.05). The urinary sodium excretion rate did not charge and the serum potassium concentration remained stable. Thirst, postural hypotension and headache were reported as adverse events (36). It appears that conivaptan is an efficient treatment of hyponatremia in the patients that require parenteral medication.
Satavaptan

Satavaptan or SR 121 463 is a potent, specific orally available vasopressin V-2 receptor antagonist first described in 1996 (37). Clinical phase III studies have been conducted in SIADH (38). Thirty-four hyponatremic patient received 25 or 50 mg orally once a day of satavaptan for 5 to 23 days, or placebo in a double-blind, randomized fashion (38). Patients maintained a fluid restriction of 1.5 L/day. In this study satavaptan increased the urinary flow rate from 1.5 to 2.5 L/day over the first 5 days of the protocol. The urinary osmolality decreased by more than 50%, the free-water clearance became positive and the hyponatremia corrected from 127 ± 5 mmol/L to 140 ± 6 (38). In the treated patients there were no significant changes of the urinary excretion rates of sodium or potassium. Despite the increased urine flow patients failed to lose weight. While this lack of a weight loss has been seen in several long term clinical studies of vaptans in the satavaptan study (38) it implies that several patients did not comply with the fluid restriction. Indeed thirst was reported as an adverse event. In view of the brisk initial diuresis it is not surprising that 10% of treated patients showed an overly rapid correction rate of their hyponatremia, i.e. > 12 mmol/L/day. No osmotic demyelisation syndrome was observed. In one arm of the protocol satavaptan was given for a duration of 1 year. In this part of the study satavaptan maintained the normonatremia and was judged to be safe. The evidence suggests that satavaptan will become an efficient oral agent for the treatment of euvolemic and hypervolemic hyponatremia.

Tolvaptan

Tolvaptan or OPC 41061 is an orally available, potent selective vasopressin-V-2 antagonist (39). In addition to experimental work, several phase II-III clinical studies have been conducted already. In the Activ trial (Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure) (40) 319 patients admitted to hospital in NYHA classes III and IV for worsening of congestion received tolvaptan (30-90 mg q.d.) or placebo orally in addition to diuretic therapy for up to 60 days. Tolvaptan increased urine output from 2.3 to 4 L/day in the initial days of the study, lowered the body weight by approximately 2 kg, improved signs and symptoms of heart failure and it normalized the serum sodium concentration in the 68 participants who had hyponatremia. There were no changes of vital signs, serum potassium, blood urea nitrogen or serum creatinine, although “renal failure” occurred in 5 treated patients and resulted in discontinuation of tolvaptan. Thirst and polyuria were the most frequently reported adverse events. In another study of tolvaptan the efficiency of the agent in correcting a hyponatremia was compared with that of a fluid restriction at 1,200 cc/day (41). The study incorporated 28 patients with euvolemic or hypervolemic hyponatremia and the treatment phase lasted up to 27 days. The dose of tolvaptan was 60 mg per day. The serum sodium concentration increased from 129 ± 3 mmol/L to 134.7 ± 3.2 in the treatment group, but it remained at 129.7 ± 3 in the placebo group. —In a large trial of 4,133 patients with heart failure 30 mg of tolvaptan or placebo was given over 9.9 months (42). Tolvaptan improved dyspnoea, body weight and edema. In patients with hyponatremia the serum sodium increased. The most frequently observed adverse events were thirst and dry mouth. However considering the large number of participating subjects and the long duration of observation it is very important that tolvaptan turned out to be a safe agent (42). —Another recent large trial—SALT I+II (Study of Ascending Levels of Tolvaptan in Hyponatremia)— with a total of 448 patients was primarily directed at hyponatremia (43). Patients with euvolemic or hypervolemic hyponatremia (128.8 ± 4.1 mmol/L) received tolvaptan 30-60 mg orally once a day or placebo in a randomized, double blind fashion. Patients were not under a fluid restriction. The study was conducted over 30 days on therapy followed by 1 week of observation after discontinuation of therapy. It was observed that tolvaptan—but not placebo—corrected the hyponatremia in all diagnostic categories and groups of severity of hyponatremia (43) (Fig. 2). After discontinuation of tolvaptan hyponatremia recurred. In the patients receiving tolvaptan the correction of hyponatremia was associated with a significant improvement of the mental health status as measured by the SF-12 questionnaire. Surprisingly body weight did not change. The most frequently encountered adverse events were: thirst, dry mouth, constipation and weakness. Overly rapid correction of a hyponatremia was not seen and there was no therapeutic overshoot into the hypernatremic rage. This outpatient study for the first time demonstrated the feasibility—and the benefits—of long term treatment of hyponatremia with an oral vasopressin antagonist.

The Treatment of Hyponatremia

What are the implications of the data discussed in the foregoing sections for the treatment of hyponatremia?

Several principles are straightforward: Hyperosmolar and normoosmolar hyponatremia suggest the presence of hyperglycemia or mannitol and action should be directed at these components. Hyponatremia in the presence of stage IV or V renal failure is probably the result of fluid intake in excess of 3 L/day and stopping the polydipsia will cure the hyponatremia. Hyponatremia in hypovolemic states—i.e. after gastrointestinal fluid losses—is best treated by infusions of isotonic saline. Such infusions will suppress ADH and enable the kidneys to excrete the excess water rapidly.

However, hyponatremia of euvolemic and hypervolemic states is the area in which future changes are imminent. The vasopressin antagonist conivaptan is already on the market; other agents are expected to follow soon. How should vasopressin antagonists be used to treat hyponatremia? What will
Figure 2. Course of the serum sodium concentration after the start of tolvaptan on day 1 (circles; n=95 patients) or placebo (squares; n=91). Therapy with tolvaptan was discontinued on day 30. Patients had chronic euvolemic or hypervolemic hyponatremia. It is demonstrated that the vaptan corrected hyponatremia into the normal range of serum sodium concentrations. (With permission from the New England Journal of Medicine).

be the advantages for the patients?

It is likely that physicians will begin to utilize vaptans in chronic mild to moderate hyponatremia because this is the area in which experience has accumulated from previous studies. In the treatment of chronic hyponatremia a slow correction rate of <12 mmol/L/day will be the intended procedure. Treatment should be decelerated or stopped when a serum—sodium of approximately 134 mmol/L—i.e. the minimally hyponatremic range—has been reached. These precautions should be observed to avoid the risk of osmotic demyelination. In the future physicians may continue to recommend fluid restrictions—but this measure will no longer be strictly required. In choosing a starting dose of any given vaptan it shall be advisable to begin with a small dose, especially in patients with SIADH, to avoid an overly rapid correction rate. It is foreseeable that the physician will have to control the serum sodium concentration repeatedly, perhaps daily in the first 3 days to titrate the dosage of the vaptan; thereafter weekly checking may suffice to keep the serum-sodium in the normal range over the first 3 weeks. Should a vaptan therapy be required over months and years specific controls of the serum-sodium should be done during episodes of fluid stress such as in the context of intercurrent diarrhea, vomiting or during heat waves.

What advantages may patients expect from vaptan treatment? It is likely that patients will be satisfied to be able to discontinue fluid restrictions. It is also to be expected that correction of hyponatremia by vaptan treatment will be followed by improvement of patients’ neural status. Furthermore in patients with chronic forms of hyponatremia vaptans should prove useful in preventing occasional precipitous decreases in the serum-sodium concentration that happen unpredictably, especially during times of fluid stress. Finally, vaptans are likely to make any treatment of hyponatremia more specific and better titratable for the physician. Hence these novel agents should turn out to be interesting therapeutic tools.

References

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