Hyponatraemia / Hyponatriämie

A. Peri

Abstract: Hyponatraemia is the most frequent electrolyte disorder in hospitalised patients and represents an important clinical and social problem. Hyponatraemia, particularly when acute and severe, can be a life-threatening condition and has been associated with an increased risk of death. However, recent evidence shows that also mild and chronic hyponatraemia can negatively affect health status by causing for instance gait disturbances, attention deficits, falls and fracture occurrence as well as bone loss. Many pathological conditions may be associated with hyponatraemia. It may be divided into hypertonic, isosmotic, or hypotonic forms, based on osmolality measurement. Attention should always be dedicated to the assessment of fluid volume, which is of pivotal importance in the diagnostic work-up, together with laboratory data. A correct diagnosis is mandatory in order to initiate appropriate treatment. Isotonic or hypertonic saline solutions are used in hypotraemic and normovolaemic/hypervolaemic hyponatraemia, respectively. Fluid restriction is generally used in asymptomatic normovolaemic/hypervolaemic hyponatraemia although its efficacy is rather poor. Vasopressin receptor antagonists, also known as vaptans, represent a new treatment option for the correction of hyponatraemia. Vaptans prevent free-water re-absorption and increase urine volume by blocking the binding of vasopressin to V2 receptors expressed in renal collecting duct cells. Therefore, they should not be used in hypovolaemic hyponatraemia. Vaptans have been shown to effectively correct serum sodium in normovolaemic and hypervolaemic hyponatraemia. While tolvaptan and conivaptan have been approved in the US for the treatment of both normovolaemic and hypervolaemic hyponatraemia, in Europe only tolvaptan was approved in 2009 for the treatment of adult patients with hyponatraemia secondary to the syndrome of inappropiate ADH secretion.

Key words: hyponatraemia, syndrome of inappropriate antidiuretic hormone secretion, syndrome of inappropriate antidiuresis, vasopressin receptor antagonists, vaptans

Introduction

Hyponatraemia, defined as a decrease in serum sodium concentration < 136 mEq/L, represents the most common electrolyte disorder in clinical practice. In particular, mild hyponatraemia (serum Na+ 130–135 mmol/L) is detected in about 20 % of hospitalised patients, whereas moderate-to-severe hyponatraemia (serum Na+ < 130 mmol/L) occurs in about 7 % of hospitalised patients [1, 2].

There is evidence that hyponatraemia is a clinical and social problem because it is a frequent alteration especially in the elderly and may strongly affect homeostasis of the brain as well as of different organs and tissues. Therefore, clinicians should keep in mind the different aspects of hyponatraemia in order to provide the best diagnostic procedures and treatment strategies for their patients. This review covers the most important issues regarding hyponatraemia from aetiopathogenesis to diagnostic and therapeutic aspects. With regard to treatment, a chapter has been dedicated to the newly available therapeutic option represented by the vasopressin receptor antagonists.

Aetiopathogenesis

Hyponatraemia can be grossly divided into 2 main groups – hypotonic and non-hypotonic forms. Non-hypotonic hyponatraemia is represented by hypertonic and isotonic hyponatraemia. The former occurs as a result of water shift from cells into the extracellular fluid that is driven by solutes confined in the extracellular compartment (eg, in hyperglycaemia). It has been estimated that each glycaemia increase of 100 mg/dl above 100 mg/dl causes a serum Na+ reduction of about 1.7 mmol/L [3]. Isotonic hyponatraemia may result from the retention in the extracellular space of large volumes of isotonic fluids that do not contain sodium (eg, absorption of

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Wasting syndrome, mineralocorticoid deficiency, salt wasting syndrome of renal solute loss (e.g., diuretic therapy, cerebral salt wasting syndrome, acute or chronic renal failure). Hypovolaemic hyponatraemia may be observed as a consequence of severe hypertriglyceridaemia or paraproteinaemia, has to be remembered. Hypovolaemia is classically associated with congestive heart failure, cirrhosis, nephrotic syndrome, and renal failure (acute or chronic). Hypervolaemic hyponatraemia is essentially represented by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and accounts for about 60% of all causes of chronic hyponatraemia; “inappropriate” meaning that it is not caused by plasma hyperosmolality or by arterial hypotension or hypovolaemia. SIADH may be caused by a number of different conditions, including for instance tumours, central nervous system disorders, and pulmonary diseases (Table 2). Ongoing drug treatment deserves particular attention because many drugs may affect water homeostasis by inducing ADH release (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors, phenothiazines, carbamazepine, vinca alkaloids, alkylating agents, opiates) and/or potentiating its effect (e.g., carbamazepine, chlorpropamide, alkylating agents, non-steroidal anti-inflammatory drugs). This syndrome has been recently referred to as “syndrome of inappropriate antidiuresis” (SIAD), following the first description of infants with clinical and laboratory features consistent with the presence of SIADH, but with undetectable ADH levels. In these patients, gain-of-function mutations in the vasopressin-type 2 (V2) receptor gene were identified [5].

**Table 1.** Main features of hypotonic hypervolaemic, normovolaemic, or hypovolaemic hyponatraemia.

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Hypotonic (dilutional) hyponatraemia is the consequence of an excess of body water relative to total body sodium stores, which can be normal, reduced, or increased [4]. It may result from excessive water intake or renal water retention. Based on extracellular fluid (ECF) volume, hypotonic hyponatraemia can be classified clinically into 3 types: hypovolaemic, hyper-volaemic, or normovolaemic [4] (Table 1).

Hypovolaemic hyponatraemia may be observed as a consequence of renal solute loss (e.g., diuretic therapy, cerebral salt wasting syndrome, mineralocorticoid deficiency, salt wasting nephropathy) or of extra-renal solute loss (e.g., vomiting, diarrhoea, pancreatitis, third-space burns). Hypervolaemic hyponatraemia is classically associated with congestive heart failure, cirrhosis, nephrotic syndrome, and renal failure (acute or chronic). Normovolaemic hyponatraemia is essentially represented by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and accounts for about 60% of all causes of chronic hyponatraemia; “inappropriate” meaning that it is not caused by plasma hyperosmolality or by arterial hypotension or hypovolaemia. SIADH may be caused by a number of different conditions, including for instance tumours, central nervous system disorders, and pulmonary diseases (Table 2). Ongoing drug treatment deserves particular attention because many drugs may affect water homeostasis by inducing ADH release (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors, phenothiazines, carbamazepine, vinca alkaloids, alkylating agents, opiates) and/or potentiating its effect (e.g., carbamazepine, chlorpropamide, alkylating agents, non-steroidal anti-inflammatory drugs). This syndrome has been recently referred to as “syndrome of inappropriate antidiuresis” (SIAD), following the first description of infants with clinical and laboratory features consistent with the presence of SIADH, but with undetectable ADH levels. In these patients, gain-of-function mutations in the vasopressin-type 2 (V2) receptor gene were identified [5]. Despite the fact that the syndrome has so far not been formally renamed, the new term SIAD should be preferred in the opinion of the author because it includes this type of patients as well.

In patients with SIAD impaired renal water excretion occurs and causes a slight increase in total body water. However, patients do not develop oedema because signs of water excess are prevented by distribution of water in both intra- and extracellular compartments of the body [4] and by sodium urinary excretion promoted mainly by the increased secretion of natriuretic peptides [6]. Normovolaemic hyponatraemia may be also associated with secondary hypocortisolism, in which the clinical and biochemical features are barely distinguishable from those of SIAD [7, 8]. In secondary hypocortisolism, the main cause of hyponatraemia seems to be an increased production of ADH, which depends mainly on loss of the tonic inhibitory effect on ADH secretion by endogenous cortisol [9]. Nevertheless, other factors can also exert a similar effect, such as nausea and hypoglycaemia [8]. Furthermore, there is evidence that hypocortisolism causes up-regulation of...
Aquaporin-2 water channels, thus reducing renal free water excretion [10]. Finally, a possible cause of normovolaemic hyponatraemia is hypothyroidism. Here, decreased cardiac output and effective arterial blood volume negatively affect glomerular filtration rate, thus determining increased proximal tubular water re-absorption and increased ADH secretion [11]. However, a study reported that the distribution of serum Na⁺ in patients with or without hypothyroidism was virtually the same [12]. This is in agreement with the calculated 0.14-mmol/l reduction of serum Na⁺ for each 10-mU/l increase of TSH.

### Clinical Features

Symptoms of hyponatraemia relate mostly to central nervous system dysfunction and are the consequence of water entry into nerve cells due to the hypotonic state [2, 4]. Symptoms depend on serum Na⁺ and, particularly, on the rate of its decline. Therefore, the degree of symptomatology exhibited by patients with hyponatraemia may be used as a surrogate for the duration of this electrolyte alteration, which may be unknown. Stupor, coma, convulsions, and respiratory arrest may be present in life-threatening, usually acute hyponatraemia, whereas headache, irritability, nausea/vomiting, mental slowing, confusion, and disorientation are more likely associated with symptomatic chronic hyponatraemia. For instance, a single-hospital study reported that stupor or coma occurred in only 6 % of patients with chronic hyponatraemia compared to 100 % with those presenting acute hyponatraemia [13]. Mild, chronic hyponatraemia has traditionally been considered as an asymptomatic or mildly symptomatic condition. However, there is increasing evidence that also mild and chronic serum Na⁺ reduction may negatively affect health status. It has been demonstrated, for instance, that apparently asymptomatic hyponatraemia is associated with falls, unsteadiness, attention deficits [14], and fracture occurrence [15, 16]. Furthermore, there is evidence suggesting that sustained hyponatraemia is associated with bone loss. This has been demonstrated in a rat model of SIAD, in which the analysis of bone architecture of excised femurs from normo- and hyponatraemic animals showed reduced bone mass in the latter group [17]. Accordingly, data from the Third National Health and Nutrition Examination Survey (NHANES III) showed that hyponatraemia remained a significant predictor of osteoporosis following adjustment for age, sex, Body Mass Index, physical activity, serum vitamin D, and diuretic use [17]. Furthermore, chronic hyponatraemia has been shown to exacerbate multiple manifestations of senescence in aged rats, including senile osteoporosis, sarcopenia, cardiac fibrosis, and hypogonadism [18]. The association between hyponatraemia and in-hospital mortality has been demonstrated in numerous studies. Noticeably, a large cohort study, which included all adult hospitalizations (n = 53,236) at an academic medical centre between 2000 and 2007, demonstrated that even mild hyponatraemia was associated with increased in-hospital mortality and that the risk of death was increased by 2.3 % for each 1-mmol/l decline of serum Na⁺ [19].

### Diagnosis

For a correct diagnostic approach several issues have to be considered: a patient’s clinical history, medications, and co-morbidities have to be taken into account. Time should be dedicated to the clinical examination of patients and, in particular, signs of volume depletion or excess should be looked for. This information will then be complemented by laboratory data: serum and urine electrolytes, glycaemia, urea, creatinine, uric acid, serum and urine osmolality, haematocrit, lipids, proteins, serum cortisol, TSH, and T4 should be measured. These data should provide enough information to establish a correct diagnosis. In particular, ECF assessment, serum, and urine osmolality are of pivotal importance in the diagnostic work-up (Figure 1). With regard to SIAD, the es-
sentential diagnostic criteria are reported in Table 3. One of the most challenging situations is represented by the differential diagnosis between SIAD and cerebral salt wasting (CSW) syndrome: the latter condition usually arises within a few days after a neurosurgical procedure, stroke, or subarachnoid haemorrhage. Some of the features of CSW are virtually identical to those of SIAD. In both conditions, hypotonic hyponatraemia, inappropriate urinary osmolality, and inappropriately high urinary sodium excretion occur. However, a fundamental difference is represented by the fact that while SIAD is classically considered a normovolaemic hyponatraemia, CSW is a hypovolaemic condition. Therefore, the presence of clinical signs of dehydration and biochemical signs of haemoconcentration will suggest the diagnosis of CSW.

“Traditional” Treatment

When approaching the treatment of hyponatraemia, physicians should try to cure the underlying disorder and this step may itself correct the electrolyte disorder: thiazide diuretics and drugs inducing SIAD should be discontinued, if possible, and hormone replacement therapy should be started in patients with hypocortisolism or hypothyroidism.

The assessment of ECF is of crucial importance in the evaluation of the correct treatment of hypotonic hyponatraemia. If hyponatraemia is present, isotonic saline (0.9 % NaCl) infusion should be initiated. Sometimes, it may be difficult to ascertain whether a patient is normovolaemic or slightly hypovolaemic. In this case, it is considered appropriate to start with an isotonic saline solution. This approach may also be considered as a diagnostic challenge because if euvalamic, rather than hypovolaemic, hyponatraemia is present, no improvement of serum Na⁺ will be achieved [6].

In case of symptomatic euvalamic or hypervolaemic hyponatraemia, infusion of hypertonic saline (3 % NaCl) represents the mainstay of treatment. Hypertonic saline is usually associated with furosemide (especially in hypervolaemic conditions), which induces diuresis equivalent to giving a one-half isotonic saline solution, thus favouring the correction of hyponatraemia [4]. The rate of correction of hyponatraemia represents a crucial point and the risk of overly rapid correction or of overcorrection should never be underestimated. Overly aggressive therapy with hypertonic saline raises serum Na⁺ to the point that extracellular fluid is more concentrated than intracellular fluid, drawing more water out of the brain cells and possibly causing the syndrome of osmotic demyelination. Most reported cases of this dramatic event occurred after rates of correction > 12 mmol/l/day, but some cases occurred also after corrections of 9 mmol/l/day. It has to be said that in most of these cases other associated risk factors for cerebral demyelination were present, such as malnutrition, hypokalaemia, or liver disease [20]. Nonetheless, it is recommended not to exceed a correction of 8 mmol/l/day. A higher initial rate of correction (2–3 mmol/l/h) is indicated only in cases of acute (< 48 h) and severe hyponatraemia (Na⁺ < 115 mmol/l) because of the high risk of severe morbidity and death. As a general rule, hypertonic saline infusion should be stopped when the patient becomes asymptomatic and/or serum Na⁺ reaches 125 mmol/l. The formula proposed by Adrogue and Madias can be used to calculate the rate of saline infusion [4].

In patients with asymptomatic hyper- or euvalamic hyponatraemia, fluid restriction represents the safe mainstay of management [4]. In SIAD, fluid restriction can be associated with a high-sodium diet (10 g/day orally). However, fluid restriction usually corrects hyponatraemia by only 1–2 mmol/l/day, even when severe (< 500 ml/day) [21]. Furthermore, fluid restriction is poorly tolerated because of increased thirst with subsequent poor compliance. Finally, fluid restriction requires the patient to excrete free water. Free water clearance by the kidney can be predicted using the urine/plasma (U/S) electrolyte ratio [22]. If the U/S ratio is ≥1, free-water clearance is negative and no excretion of free water is expected.

Other options for the treatment of eu- or hypervolaemic hyponatraemia, such as demeclocycline, urea, or lithium, are considered suboptimal for several reasons, including variable efficacy, slow responses, and toxic effects [23, 24].

The New Frontier: Vasopressin Receptor Antagonists

A new area for the treatment of hyponatraemia was started with the development of non-peptide vasopressin receptor antagonists, the so-called vaptans. In particular, vaptans block ADH binding to V₂ receptors expressed in renal collecting duct cells. This inhibits the synthesis and transport of aquaporin-2 water channel proteins into the apical membrane of these cells, thus preventing free-water re-absorption and causing increased urine volume [25]. Therefore, vaptans cause water diuresis, namely aquareas, thus increasing serum Na⁺. In 1993, the first successful use of a non-peptide V₂ receptor antagonist was reported in humans [26].

Several vaptans have been developed and tested in humans, including tolvaptan, conivaptan, lixivaptan, mozavaptan, satavaptan, and RWJ351647 [27]. Because of their mechanism of action, vaptans are not to be used in hypovolaemic hyponatraemia. Currently, only one selective V₂ receptor antagonist, tolvaptan, is available on the market in Europe and in the US. In Europe, tolvaptan (oral tablet) was approved by

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**Table 3. Essential diagnostic criteria of SIAD.**

| Hyponatraemia (serum Na⁺ < 136 mmol/l) |
| Plasma hypo-osmolality (< 275 mOsm/kg) |
| Urine osmolality > 100 mOsm/kg |
| Clinical normovolaemia |
| No clinical signs of hypovolaemia (orthostatic decreases in blood pressure, tachycardia, decreased skin turgor, dry mucous membranes) |
| No clinical signs of hypervolaemia (oedema, ascites) |
| Increased urinary sodium excretion (> 40 mmol/l with normal salt and water intake) |
| Absence of other potential causes of euvolaemic hypo-osmolality: exclude recent diuretic use, renal disease, hypocortisolism, and hypothyroidism |
the European Medicines Agency (EMA) on August 9, 2009, with the indication “treatment of adult patients with hyponatraemia secondary to SIADH”. In the US, tolvaptan was approved by the Food and Drug Administration (FDA) on May 29, 2009, for the “treatment of clinically significant hypervolaemic and euvo-lae mic hyponatraemia”, thus including patients with heart failure and cirrhosis. Another vaptan with partial affinity also for the V1 receptor, conivaptan (injection formulation), was approved on December 29, 2005, in the US for the “treatment of euvo-lae mic and hypervolaemic hyponatraemia in hospitalised patients”.

Because this review addresses endocrinologists and because only tolvaptan is available at this time as an oral formulation for the treatment of hyponatraemia secondary to SIAD, the main trials regarding this drug, which included patients with SIAD, and the lessons we have learned on clinical grounds in the last couple of years will be summarised here.

The efficacy of tolvaptan in patients with eu- or hypervolaemic hyponatraemia was evaluated in 2 multicentre, randomised, double-blind, placebo-controlled trials, the Study of Ascending Levels of Sodium in hyponaTraemia 1 and 2 (SALT-1 and SALT-2) [28]. Serum Na+ increased to a greater extent in the tolvaptan group (n = 225, 15–60 mg/day) than in the placebo group (n = 223) during the first 4 days and at completion of the treatment period (30 days). At baseline, this difference was present both in patients with mild (130–135 mmol/l) or moderate/severe (< 130 mmol/l) hyponatraemia. Increased thirst and dry mouth were the most commonly observed side effects in agreement with the aquaretic effect of the drug. An overly rapid correction of hyponatraemia or overcorrection occurred in < 2 % of patients. Interestingly, a combined analysis of SALT-1 and SALT-2 revealed that patients treated with tolvaptan reported a significant increase in the score of the mental component of the SF-12 health survey from baseline to day 30. A subsequent subgroup analysis of patients with SIAD (n = 110) in SALT-1 and SALT-2 confirmed a greater increase in serum Na+ in patients in the tolvaptan group compared to the placebo group [29]. In SIAD patients, the SF-12 Health Survey revealed a significantly positive effect of tolvaptan on the physical component, but a near-significant trend was also observed on the mental component.

The long-term use of tolvaptan was assessed in another subsequent trial, SALTWATER, a multicentre, open-label extension of SALT-1 and SALT-2 [30]. In this trial, hyponatraemic patients (n = 111) were treated with tolvaptan for a mean follow-up of almost 2 years. Prompt normalisation of serum Na+ was reported and normal values were maintained throughout the observation period. The safety of tolvaptan was also confirmed in this trial and an excessive rate of correction or hypernatraemia was rarely observed.

In European clinical practice, the use of tolvaptan may be considered a valuable option in patients with hyponatraemia due to SIAD who have moderate symptoms (eg, confusion, disorientation, nausea, unstable gait) as an alternative to hypertonic saline infusion. In addition, tolvaptan may be effectively used in SIAD patients with mild symptoms related to hyponatraemia (eg, mild neurocognitive alterations, depression) or in asymptomatic patients, if fluid restriction fails or is not tolerated [31, 32] (Figure 2). In some instances, tolvaptan may also be considered as the first-choice treatment to correct hyponatraemia. This can be the case in surgical or oncological patients in order to achieve rapid correction and avoid treatment delay. Tolvaptan may be also used as the first-choice option in hyponatraemic patients with SIAD, when the kidneys are not expected to excrete solute-free water (U/S electrolyte ratio ≥ 1) or as a trial to treat symptoms likely caused by hyponatraemia. On the other hand, it has to be kept in mind that in patients with severely symptomatic hyponatraemia (eg, respiratory distress, seizures, coma) active treatment with hypertonic saline remains the recommended treatment option.

When using vaptans, the general rules regarding the rate of correction of serum Na+ should be applied and frequent electrolyte monitoring is required. There is evidence, for instance, that in patients with very low serum Na+ at baseline (≤ 120 mmol/l) greater responses may occur [33] and, recently, both the EMA and FDA have reinforced recommendations about fluid and electrolyte monitoring in patients treated with vaptans. In case of an excessive increase in serum Na+, administration of the drug should be stopped or the dose should be reduced; furthermore, the use of hypotonic fluid should be considered [23].
Hyponatraemia

Conclusions and Practical Relevance

Hyponatraemia is a biochemical sign that can be associated with a number of different pathological conditions. Hyponatraemia per se represents a problem of clinical and social relevance and a correct diagnostic work-up should be performed in order to provide the most appropriate treatment to patients. Although extensive comparative research of vaptans vs other therapies and analyses of patients treated with these drugs are needed to better define their real effectiveness in clinical practice, vaptans appear to be an additional useful and safe tool, if appropriately used, for the correction of hyponatraemia.

Relevance for the Praxis

Hyponatraemia is a biochemischer Zustand, der mit einer Vielzahl verschiedenster pathologischer Zustandsbilder in Verbindung gebracht wird. Die Hyponatraemia per se ist ein Problem von klinischer und sozialer Relevanz und ein korrektes diagnostisches Work-up sollte durchgeführt werden, um den Patienten die beste passende Behandlung bieten zu können. Obwohl die ausführliche vergleichende Forschung an Vapten im Vergleich zu anderen Therapieverfahren sowie Analysen der mit diesen Substanzen behandelten Patienten notwendig ist, um deren wirkliche Effektivität in der klinischen Praxis definieren zu können, scheinen Vapten bei korrekter Anwendung ein zusätzliches, sinnvolles und sicheres Mittel zur Korrektur einer Hyponatraemia zu sein.

Conflict of Interest

The author is on the Otsuka Pharmaceutical advisory board for tolvaptan and has received honorary from Otsuka Pharmaceutical for speaking at symposia.

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