

SIADH and hyponatraemia: foreword

Donal O'Donoghue¹ and Anu Trehan²

¹Department of Nephrology and ²Department of Acute Medicine, Salford Royal Hospital, Salford, UK

Correspondence and offprint requests to: Donal O'Donoghue; E-mail: donal.o'donoghue@srft.nhs.uk

Abstract

Hyponatraemia is common, affecting about one in five of all hospitalized patients. Minor degrees of chronic hyponatraemia cause cognitive and motor impairment, and severe hyponatraemia is associated with substantial morbidity and mortality. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a common cause of hyponatraemia and is often poorly understood and inappropriately treated. Clinical evaluation and simple biochemical assessment should guide management. The introduction of vasopressin antagonists, or vaptans, into clinical practice heralds the beginning of a new and exciting era for this important group of disorders.

Keywords: hyponatraemia; SIADH; vasopressin; vasopressin-receptor antagonists

Introduction

Hyponatraemia, defined as an excess of water in relation to sodium in the extracellular fluid, is the most common electrolyte disorder in hospitalized patients [1]. It is usually mild and relatively asymptomatic, but acute severe hyponatraemia can cause substantial morbidity and mortality [2]. In addition, overly rapid correction of chronic hyponatraemia can cause severe neurologic defects and even death [3]. Hyponatraemia is, therefore, important to appreciate, both because of its potential morbidity and because it can be a marker of serious underlying disease. Evidence is now emerging that even minor degrees of chronic hyponatraemia are associated with significant motor and cognitive impairment [4].

Hyponatraemia (serum sodium <135 mmol/l) occurs in 15–22% of hospitalized patients [5]. The incidence of moderate and severe hyponatraemia is lower occurring in 1–7% of hospitalized patients [5]. It is known that severe hyponatraemia is actually acquired in hospital in approximately half of those who develop a serum sodium <125 mmol/l [1]. Certain populations are at increased risk, including the elderly, especially nursing home residents [2].

This common disorder remains incompletely understood and often inappropriately managed because of its associ-

ation with a myriad of underlying disease states, and its multiple aetiologies with different pathophysiologic mechanisms [5]. It is likely that the underlying disorders divert attention from hyponatraemia. It can be difficult to know to what extent symptoms and morbidity are caused as a direct result of the hyponatraemia, the underlying conditions or a combination of both. In particular, in hospital-acquired hyponatraemia, which is frequently multi-factorial, there appears to be a low recognition of deteriorating hyponatraemia resulting in inadequate or delayed management. Movig *et al.* [6] reviewed the discharge diagnosis of 'hyponatraemia' in 2632 cases and identified a low recognition rate, with only 30% of patients with severe hyponatraemia accurately classified. Hoorn *et al.* [7] have suggested that better management may be achieved by physician education and development of preventative hospital systems. The development of evaluation and treatment strategies for hyponatraemia must take into account the heterogeneity of the condition and the marked differences in symptomatology and clinical outcomes based on the acuteness or chronicity of the hyponatraemia.

The articles in this supplement begin to address this educational gap. Despite the areas of uncertainty in management, clinicians should not overlook this very common condition. Knowledge of the syndrome of inappropriate antidiuretic hormone (SIADH), risk factors for development and the underlying mechanisms is essential for all physicians [3]. Conventional therapy for hyponatraemia is limited, but the introduction of vasopressin-receptor antagonists offers the possibility of an effective method to treat hyponatraemia, by virtue of their unique aquaretic effect to selectively increase solute-free water excretion by the kidneys [3].

Clinical evaluation of hyponatraemia

Serum sodium concentration is the main determinant of plasma osmolality, and most hyponatraemic states are characterized by elevated plasma levels of arginine vasopressin (AVP) [5]. SIADH is the most frequent cause of hyponatraemia, although hyponatraemia associated with volume depletion of the extracellular fluid also occurs commonly.

The clinical assessment of the patients' extracellular fluid (ECF) volume status coupled with a history and examination to identify potential drug-related hyponatraemia and underlying predisposing conditions often permits a sufficient categorization of the underlying aetiology to allow initial treatment and to inform the plan for further diagnostic evaluation [3]. The three major classifications of hypotonic hyponatraemia are based on the patients' ECF volume status: hypovolaemic hyponatraemia, euvolaemic hyponatraemia and hypervolaemic hyponatraemia.

When the origin of the hyponatraemia is not obvious, the possibility of pseudohyponatraemia should be considered. Marked elevation of either lipids or proteins in plasma can cause artificial decrease in serum sodium because of the larger relative proportion of plasma volume that is then occupied by the excess lipids or proteins. In such cases, directly measured plasma osmolality will be normal [8].

Hyponatraemia with normal or even raised osmolality can also occur when high levels of other non-cell permeant solutes are present in the plasma. In most instances, these situations should not lead to diagnostic confusion because the cause is obvious. This situation is most commonly seen with hyperglycaemia when the accompanying glucose-induced osmotic diuresis can result in hypertonicity despite hyponatraemia [9]. Radio contrast agents, mannitol, sorbitol, glycerol, maltose and glycine also act as osmotic agents that withdraw water from the intracellular compartment [10]. Glycine infusion into the bladder or uterus during transurethral resection of the prostate (TURP) or endoscopic uterine surgery can lead to absorption of a large volume of fluid with resultant hyponatraemia and development of the 'post-TURP syndrome' [11]. Clinical manifestations include headache, mental depression, visual disturbance, blindness, seizures, cardio respiratory arrest and death and are probably attributable to the direct toxicity of the absorbed glycine and its metabolites.

However, in most clinical situations hyponatraemia is accompanied by significant hypo-osmolality indicating excess water relative to solute/sodium in the ECF compartment [5]. This can be produced either by excess body water, resulting in a dilution of remaining body solute, or by depletion of body solute/sodium relative to body water. This segregation into dilutional (euvolaemic and hypervolaemic) or depletional (hypovolaemic) is a conceptually useful paradigm to the understanding of the underlying mechanisms and pathogenesis of hyponatraemia [3]. In reality, many hyponatraemic states involve components of both solute depletion and water retention but the balance should determine the appropriate therapy in particular clinical situations.

Patients with clinical signs of volume depletion (e.g. orthostatic drop in blood pressure, tachycardia) should be considered hypovolaemic and those with evidence of volume expansion (oedema or ascites) hypervolaemic, unless there are alternative explanations for these findings.

The clinical setting and other laboratory clues to the presence of volume depletion, such as raised urea or creatinine, may provide corroboration. When the clinical assessment is equivocal, a trial of volume expansion can be helpful in establishing the type of hyponatraemia, and will be therapeutic if volume depletion is the cause of the hypona-

Table 1. Aetiologies of depletional (hypovolaemic) hyponatraemia

Renal loss of sodium with water retention	Extrarenal loss of sodium with water retention
<ul style="list-style-type: none"> • Diuretic therapy • Cerebral salt wasting • Mineralocorticoid deficiency <ul style="list-style-type: none"> (a) Autoimmune <ul style="list-style-type: none"> (i) Adrenal only (ii) Polyglandular endocrinopathy (b) Adrenal haemorrhage <ul style="list-style-type: none"> (i) Meningococcaemia (ii) Idiopathic (c) Infection <ul style="list-style-type: none"> (i) Tuberculosis (ii) Fungus (iii) CMV (d) Adrenal enzyme deficiencies (congenital adrenal hyperplasia) • Salt-wasting nephropathy • Bicarbonaturia, glucosuria, ketonuria 	<ul style="list-style-type: none"> • Gastrointestinal losses <ul style="list-style-type: none"> (a) Vomiting (b) Diarrhoea • Third space losses <ul style="list-style-type: none"> (a) Bowel obstruction (b) Pancreatitis (c) Muscle trauma (b) Burns • Sweat losses <ul style="list-style-type: none"> (a) Endurance exercise

CMV = cytomegalovirus.

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traemia. After a 0.5–1 l infusion of isotonic (0.9%) NaCl, patients with hypovolaemic hyponatraemia will begin to correct their hyponatraemia without developing signs of volume overload [5]. Conversely, in patients with SIADH the serum sodium will remain unchanged or decrease.

A spot urine sodium concentration can be a useful adjunct to categorizing the ECF volume status. If the patient is volume depleted, his/her urine sodium concentration should be <30 mmol/l unless the kidney is the site of the sodium loss. In those with euvolaemic hyponatraemia, the urine sodium level is usually ≥ 30 mmol/l unless they have become secondarily sodium depleted. In states of volume expansion with decreased effective arterial blood volume e.g. heart failure, cirrhosis, renal failure or nephrotic syndrome, the spot urine is usually low (<30 mmol/l) [3]. The concomitant use of diuretics can of course make interpretation of urinary sodium measurements difficult.

There are a whole range of conditions that can cause each of the three types of hypotonic hyponatraemia (see Tables 1 and 2) [3]. Investigation and medium- to long-term treatment can be planned using this classification. Adopting such a systematic approach to clinical evaluation will help address some of the deficiencies in care that previous studies have highlighted [3,5].

Management challenges in SIADH

In contrast to hyponatraemia secondary to volume depletion, which is usually corrected by treatment of the underlying condition and intravenous fluids, the management of dilutional hyponatraemia remains a challenge in many clinical settings [3,5]. The only definitive treatment of SIADH is elimination of its underlying cause. Most cases caused by curable malignant disease resolve with effective antineoplastic therapy, and most of those due to medication resolve promptly when the offending agent is discontinued [5] However, in many instances, including

Table 2. Aetiologies of dilutional (euvoalaemic and hypervolaemic) hyponatraemia

Impaired renal free water excretion

- Euvolaemic
 - (a) SIADH
 - (i) Tumours
 - Pulmonary/mediastinal (bronchogenic carcinoma, mesothelioma, thymoma)
 - Nonchest (duodenal carcinoma, pancreatic carcinoma, ureteral/prostate carcinoma, uterine carcinoma, nasopharyngeal carcinoma, leukaemia)
 - (ii) CNS disorders
 - Mass lesions (tumours, brain abscesses, subdural haematoma)
 - Inflammatory diseases (encephalitis, meningitis, systemic lupus, acute intermittent porphyria, multiple sclerosis)
 - Degenerative/demyelinative diseases (Guillain–Barré syndrome; spinal cord lesions)
 - Miscellaneous (subarachnoid haemorrhage, head trauma, acute psychosis, delirium tremens, pituitary stalk section, transphenoidal adenectomy, hydrocephalus)
 - (iii) Drug induced
 - Stimulated AVP release (nicotine, phenothiazines, tricyclics)
 - Direct renal effects and/or potentiation of AVP antidiuretic effects (DDAVP, oxytocin, prostaglandin synthesis inhibitors)
 - Mixed or uncertain actions (ACE inhibitors, carbamazepine and oxcarbazepine, chlorpropamide, clofibrate; clozapine, cyclophosphamide, 3,4-methylenedioxymethamphetamine [“Ecstasy”], omeprazole; serotonin reuptake inhibitors, vincristine)
 - (iv) Pulmonary diseases
 - Infections (tuberculosis, acute bacterial and viral pneumonia, aspergillosis, empyema)
 - Mechanical/ventilatory (acute respiratory failure, COPD, positive pressure ventilation)
 - (v) Other
 - AIDS and ARC
 - Prolonged strenuous exercise (marathon, triathlon, ultramarathon, hot-weather hiking)
 - Senile atrophy
 - Idiopathic
 - (b) Glucocorticoid deficiency
 - (c) Hypothyroidism
 - (d) Decreased urinary solute excretion
 - (i) Beer potomania
 - (ii) Very low protein diet
- Hypervolaemic
 - (a) CHF
 - (b) Cirrhosis
 - (c) Nephrotic syndrome
 - (d) Renal failure
 - (i) Acute
 - (ii) Chronic

Excessive water intake

- Primary polydipsia
- Dilute infant formula
- Freshwater drowning

ACE = angiotensin-converting enzyme; AIDS = acquired immune deficiency syndrome; ARC = AIDS-related complex; AVP = arginine vasopressin; CHF = congestive heart failure; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; DDAVP = desmopressin acetate; SIADH = syndrome of inappropriate antidiuretic hormone secretion.
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malignancy, the underlying condition is chronic, hyponatraemia has been present for an indeterminate duration and there may be varying degrees of mild neurological symptomatology. The cases presented by Lubbe *et al.* [12] and the review of treatment options by Zietse *et al.* [13] in the accompanying articles in this supplement outline the current treatment strategies and identify some of the areas of uncertainty in the management of SIADH. Currently, treatment failures are common in this group of patients. In the elderly, physicians generally tolerate the presence of mild hyponatraemia if water restriction does not result in normalization of serum sodium. Unfortunately, there are few randomized controlled trials to guide therapy, but the concept of asymptomatic hyponatraemia has recently been challenged by epidemiological evidence from a number of studies in Europe and the USA [14,15]. Decaux reported a series of 122 consecutive patients hospitalized with mild hyponatraemia, ~21% of whom were admitted with falls [15]. After controlling for age, sex and other known risk

factors for falls, the adjusted odds ratio for falls in patients with hyponatraemia was 67, compared with a control group. The same authors have demonstrated that clinically asymptomatic patients with chronic hyponatraemia have attention deficits and gait abnormalities that were clinically unrecognized by the patients and their physicians [4]. Arieff and Ayus [16] reported pre-operative hyponatraemia in 7.2% of patients with hip fractures.

Hyponatraemia has also been associated with negative outcomes in many chronic diseases, most notably in patients with congestive cardiac failure [3]. One study of 161 patients with severe congestive heart failure found hyponatraemia to be a significant predictor of cardiovascular mortality, with 69% of hyponatraemic patients dying within 24 months compared with 40% of patients without baseline hyponatraemia ($P < 0.001$) [17]. Similarly, in a study examining admission hyponatraemia among 4123 geriatric patients, in-hospital mortality was found to be 16% amongst patients with admission hyponatraemia versus 8% amongst

those without this condition [18]. In the general adult hospitalized population, Anderson *et al.* found that mortality rates were 60-fold higher in patients with even asymptomatic hyponatraemia compared to normonatraemic patients [19]. The degree to which this strong association between hyponatraemia and negative outcomes is causally related to the hyponatraemia and might be improved with more effective therapies is not known.

Hospitalization figures relating to hyponatraemia in Europe are not accurately known; however, data in the USA show that there are ~1 million hospitalizations per year with a principal or secondary discharge diagnosis of hyponatraemia [20], as well as an estimated 105 000–120 000 annual emergency room visits and 1.4–3.4 million annual office visits for hyponatraemia. The direct cost for treating hyponatraemia in the USA on an annual basis was estimated to range between \$1.6 billion and \$3.6 billion. The majority, ~70%, of the additional costs were in those whose hospitalization was prolonged due to hyponatraemia [20].

Next steps

Vasopressin-receptor antagonists have long been anticipated as an effective method to treat hyponatraemia by virtue of their unique effect to selectively increase solute-free water excretion by the kidneys. A range of studies have shown that these agents correct and maintain serum sodium levels in patients with hypervolaemic and euvoalaemic hyponatraemia in the long and short term [21–23]. Information regarding these studies is discussed in Professor Zietse's paper 'Current and future treatment options in SIADH' later in this supplement [13].

The vaptans (for *vasopressin antagonists*) herald the beginning of a new and exciting era in the management of hyponatraemia and have rekindled interest in this important group of disorders. There is no need for therapeutic nihilism in the management of hyponatraemia. Our use of these agents and the optimal place for conventional therapy needs to be guided by a systematic approach to clinical evaluation and an existing knowledge of the pathophysiology of hyponatraemia informed by the results of well-constructed clinical trials to examine the impact of these agents on patient experience, clinical outcomes and costs of health care delivery [3].

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