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Nephrology Dialysis Transplantation

# The clinical challenge of SIADH—three cases

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## Abstract

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) remains a challenging disorder to diagnose and treat. Three cases are presented to illustrate these challenges. The first two cases had drug-induced SIADH secondary to a selective serotonin reuptake inhibitor (for depression) or carbamazepine (for trigeminal neuralgia). The third case had SIADH possibly secondary to bronchiectasis. The lowest serum sodium concentrations ranged between 118 and 124 mmol/L in the three cases. Hyponatraemia was not acute and severe symptoms were absent. However, several mild neurological symptoms were present. In the first case, hyponatraemia likely contributed to a fall, which resulted in a fracture of the odontoid process of the axis. The other two cases also had gait disturbances, in addition to nausea, headache, impaired memory, difficulty concentrating and confusion. In at least two of the cases, the underlying cause of SIADH was impossible to reverse. Traditional treatment for SIADH with fluid restriction and demeclocycline failed, caused side effects or increased duration of hospital stay. These examples suggest a need for better treatment options. The introduction of the vasopressin-receptor antagonists for SIADH may be a welcome new therapy to overcome some of these challenges.

**Keywords:** bronchiectasis; carbamazepine; demeclocycline; selective serotonin reuptake inhibitor; vasopressin-receptor antagonists

## Introduction

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is one of the more common causes of hyponatraemia and is characterized by an inability to dilute urine despite hypoosmolality [1]. Both diagnosis and treatment of SIADH can be difficult. Below, we present three cases to illustrate the current challenges of SIADH.

## Case 1

A 78-year-old woman was brought to the hospital after a fall on the stairs. She had a past medical history of hyper-

tension and atrial fibrillation, for which she took a calcium channel blocker, a coumarin derivative and a beta blocker. A selective serotonin reuptake inhibitor (SSRI), sertraline (40 mg q.d.), had been prescribed by her general practitioner 2 months before, because of complaints of depression following the death of her son. She reported climbing a flight of stairs with a glass of water in her hand. The next moment she was lying on the ground not remembering what had happened. Before the fall she experienced thirst for a number of days, but did not report other complaints. She apparently had a normal diet with normal salt intake. At presentation, she indicated severe pain in her head and neck. On physical examination, she had several bruises on her head and she was disoriented to time and place. The blood pressure was 120/90 mm Hg, and she had an irregular pulse of 80 beats per minute. She did not have apparent signs of extracellular fluid volume contraction. A computed tomography scan of her cervical spine revealed a fracture of the odontoid process of the axis (type III according to the Anderson and d'Alonzo classification), which was treated with a halo-frame and physiotherapy. By serum chemistry, hyponatraemia was found (Table 1). Because of the known association between sertraline and hyponatraemia [2], and because her biochemical profile suggested SIADH (Table 1), sertraline was discontinued and she was placed on a fluid restriction (1.0 L/day). Serum sodium rose to 134 mmol/L in 5 days. Physical rehabilitation was commenced, and serum sodium was checked periodically and remained normal (137–139 mmol/L). She was able to cope without the antidepressant.

## Case 2

A 53-year-old woman was referred to our outpatient clinic because of recurrent complaints of nausea. In addition, her general practitioner had repeatedly found a low serum sodium concentration. She had a previous history of trigeminal neuralgia, which had proved difficult to treat. Previously, pregabalin, gabapentin and oxcarbazepine had been tried, but either gave serious side effects or insufficient pain relief. The option of microvascular decompression had been discussed with the neurosurgeon, but had been deferred

**Table 1.** Clinical and laboratory characteristics of three SIADH cases

|  | Case 1 | Case 2 | Case 3 | References |
|---|---|---|---|---|
| **Clinical data** | | | | |
| Gender and age | 78, female | 53, female | 66, male | |
| Presentation | Fall | Nausea, hyponatraemia | Confusion, headache, unsteadiness | |
| Cause of SIADH | Sertraline | Carbamazepine | Bronchiectasis? | |
| **Serum values** | | | | |
| Sodium, mmol/L | 125 | 128 | 118 | 136–145 |
| Potassium, mmol/L | 4.2 | 4.3 | 3.9 | 3.5–5.1 |
| Creatinine, μmol/L | 46 | 56 | 60 | 55–90 (♀) 65–115 (♂) |
| Urea, mmol/L | 4.7 | 4.5 | 2.8 | 2.5–7.5 |
| Uric acid, mmol/L | 0.18 | 0.15 | - | 0.2–0.42 |
| Osmolality, mOsm/kg | 255 | 265 | 249 | 275–300 |
| **Endocrine tests** | | | | |
| TSH, mU/L | 2.10 | 4.07 | 0.9 | 0.4–4.3 |
| Cortisol, nmol/L | 1095 | 287 | 327 → 693[a] | 200–800[a] |
| **Urine values** | | | | |
| Sodium, mmol/L | 44 | 65 | 58 | – |
| Osmolality, mOsm/kg | 523 | 426 | 547 | – |

[a]Before and 30 minutes after 250 μg synthetic ACTH. The normal response is a rise in serum cortisol to ≥ 500 nmol/L after 60 minutes. Reference for cortisol is for ~9.00 am.
TSH, thyroid-stimulating hormone; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

for the time being. Her neurologist had accepted hyponatraemia as an unavoidable side effect of carbamazepine, one of the few drugs that could relieve her trigeminal neuralgia. It was currently under control by a combination of carbamazepine (400 mg b.i.d.) and amitriptyline (10 mg q.d.). She complained of nausea, forgetfulness and difficulty concentrating. Most of these complaints had been present for a number of years. She also admitted gait instability during her weekly game of tennis. She had a normal diet, and was believed to have normal water and salt intake. Her blood pressure was 120/80 mm Hg, her pulse was 60 beats per minute. Physical examination was unremarkable and she neither had oedema nor orthostatic changes (clinical euvolaemia). Her previous laboratory tests showed chronic hyponatraemia with serum sodium levels fluctuating between 124 and 135 mmol/L since 2004. Her current laboratory results are shown in Table 1. Because of the biochemical data (Table 1) together with carbamazepine and amitriptyline use, SIADH appeared the most obvious diagnosis, although adrenal insufficiency could not formally be excluded on the basis of a random cortisol value. Because the neurologist determined that the carbamazepine was essential to the patient, we advised the patient to limit fluid intake to 1 L/day, and to contact the hospital in situations of fever, diarrhoea, vomiting or the prescription of a new drug. We explained the likely connection between her symptoms and her chronic hyponatraemia to her neurologist, and advised to check serum sodium levels at regular intervals. Because this patient was recently seen in our outpatient clinic, the response in serum sodium and symptomatology to fluid restriction remains to be determined.

## Case 3

A 66-year-old man presented to the emergency room with symptoms of confusion, unsteadiness and headaches. He had a previous history of psoriasis and frequent respiratory tract infections (two to three per year), which often required antibiotic treatment, but for which no formal diagnosis had been made. He had a 30 pack year smoking history. He did not use medication. Based on his symptoms, his general practitioner suspected a brain tumour or early-onset dementia. His blood pressure was 126/80 lying and 130/84 standing, with a regular pulse of 88 bpm. He had no oedema and his jugular venous pressure was normal. Further physical examination was unremarkable.

He turned out to have hyponatraemia of 118 mmol/L (Table 1). Computed tomography was performed and revealed pulmonary bronchiectasis (a new finding), while the head and abdomen scans were normal. Subsequent bronchoscopy was normal, and sputum cytology and brushings were negative for cancer and tuberculosis. In an additional work-up for hyponatraemia, hypothyroidism and adrenal insufficiency were excluded (Table 1). Therefore, based on clinical euvolaemia and the biochemical data (Table 1), the working diagnosis was SIADH possibly secondary to bronchiectasis. He was placed on fluid restriction (800 mL/day), which increased serum sodium to 126 mmol/L in 6 days. In parallel, his gait improved, confusion and headaches disappeared, whereas his memory still remained impaired. He was discharged with the advice to maintain the fluid restriction, and visited the outpatient clinic two weeks later. He reported a recurrence of headaches. His serum sodium concentration had fallen to 122 mmol/L. Alternative treatment for SIADH was started in the form of demeclocycline (300 mg three times daily). Two weeks later serum sodium had risen to 130 mmol/L, and the patient felt well again with improved memory. However, another two weeks later, he developed polyuria and polydipsia with a serum sodium concentration of 152 mmol/L. Demeclocycline was temporarily discontinued, and then reintroduced at half dose, producing a serum sodium of 140 mmol/L. Despite achieving this stable situation, demeclocycline had to

be withdrawn again, because PUVA-therapy (psoralene and ultraviolet radiation) was started for psoriasis, and demeclocycline is very photosensitizing. Consequently, hyponatraemia reemerged with a serum sodium of 126 mmol/L despite a fluid restriction of 1000 mL/day. His serum sodium currently remains in the range between 121–129 mmol/L, and he continues to experience headaches, cognitive decline (<126 mmol/L) and gait unsteadiness (<122 mmol/L).

## Discussion

The three cases represent common clinical examples of SIADH, with which most clinicians may be familiar. Below, the mechanisms of SIADH in the three cases will be discussed briefly, followed by a discussion of the clinical dilemmas that SIADH posed in these patients.

### Mechanisms of SIADH

SSRI-induced hyponatraemia (Case 1) was first reported with the use of sertraline in 1993 [3]. In 1996, Liu *et al.* reviewed 736 cases of SSRI-induced hyponatraemia (30 published cases, 706 cases reported to monitoring bodies and the pharmaceutical industry). They found that hyponatraemia may occur with all major SSRIs, including fluoxetine, paroxetine, sertraline and fluvoxamine [4]. Fabian *et al.* conducted a prospective study in 75 subjects who started with paroxetine after a major depressive episode had been diagnosed [5]. Hyponatraemia developed in nine patients (12%). Their serum sodium concentrations fell from $137 \pm 2$ to $128 \pm 2$ mmol/L, and this took $9.3 \pm 4.7$ days. Interestingly, vasopressin levels in normonatraemic and hyponatraemic patients were normal, and did not differ between groups. However, 'normal' vasopressin levels during hypotonicity could still be considered inappropriate, because hypotonicity should normally suppress vasopressin. In rats, chronic administration of sertraline did increase levels of vasopressin and oxytocin, suggesting hyponatraemia to be a central phenomenon [6]. In contrast, in a rat-model of fluoxetine-induced hyponatraemia, vasopressin levels remained unchanged [7]. Instead, a 40% increase in the expression of the water channel aquaporin-2 water in the renal collecting duct was shown, suggesting a direct renal effect of the drug.

The reported incidence of carbamazepine-induced hyponatraemia (Case 2) ranges between 4 and 22% [8,9]. For oxcarbazepine, the keto-analogue of carbamazepine, the incidence appears even higher with 51% [10]. Definite risk factors remain unclear, but age, serum carbamazepine levels and concomitant drugs affecting electrolyte balance have all been implicated [11]. Carbamazepine was first marketed as a drug to treat trigeminal neuralgia (formerly known as *tic douloureux*) in 1962. The first two cases of carbamazepine-induced hyponatraemia were reported in 1977 [12,13]. Since, several mechanisms have been proposed for carbamazepine-induced hyponatraemia [14], and they are probably not mutually exclusive. The first two case reports found elevated levels of vasopressin (1.7 and 4.0 pg/mL with serum osmolalities of 261 and 257 mOsm/kg, respectively) [12,13], suggesting the most simple explanation, namely that carbamazepine stimulates vasopressin secretion. In another report, however, Meinders *et al.* had described the opposite, a decrease in vasopressin with carbamazepine; they therefore suggested a renal effect [15]. This would be in agreement with the finding that carbamazepine is able to improve the polyuria of central diabetes insipidus, in which endogenous vasopressin secretion is virtually absent [16]. Stephens *et al.* proposed a combined central and renal effect [17]. In their experiments in healthy volunteers, they showed that with carbamazepine vasopressin levels *rose less* during water deprivation and *fell less* during water loading. Thus, they concluded that 'under the influence of carbamazepine the osmoreceptors become lazy' [17]. However, they also observed impaired diuresis during carbamazepine, despite similar vasopressin concentrations at peak diuresis with carbamazepine and control. They therefore proposed that carbamazepine also increased renal sensitivity to 'normal' vasopressin levels. Because carbamazepine-induced water retention did not suppress vasopressin, this was additional evidence that resetting of the osmoreceptors must also have occurred. Toad bladder experiments, however, were unable to confirm a renal effect, because carbamazepine did not affect osmotic water flow nor did it potentiate the response to vasopressin [18].

The use of amitriptyline may also have contributed to hyponatraemia in Case 2. The mechanism of amitriptyline in hyponatraemia remains elusive. The evidence here consists solely of case reports [19,20].

Although cited in reviews [21], the mechanism of SIADH in bronchiectasis is also unclear. It probably shares features with other pulmonary diseases that can cause SIADH, including cystic fibrosis [22], pneumonia [23], asthma [24] and chronic obstructive pulmonary disease [25]. Several pathophysiological scenarios have been discussed for SIADH in these diseases, including a reset osmostat, an effect on baroreceptors or a direct effect of hypercapnia on vasopressin release [26,27]. Since many of these pulmonary diseases are also characterized by infection, the relation between the acute phase response and hyponatraemia, which is becoming increasingly clear [28], is also of interest. In fact, recent animal data show an intriguing interaction between interleukin-6 and vasopressin release [29]. Because data on bronchiectasis and SIADH are limited, it is important to emphasize that it is difficult to be sure about their relationship in Case 3. Alternatively, other causes of SIADH may become apparent over time, or SIADH may turn out to be idiopathic.

### Challenges of SIADH

The three cases illustrate several of the aspects of SIADH and its treatment that were discussed in the previous articles of this supplement. All three patients had chronic hyponatraemia, and severe symptoms such as seizures and coma were absent. However, they did have other more subtle neurological symptoms to which hyponatraemia likely contributed. Hyponatraemia may have caused the fall in Case 1, and the headache, nausea, attention deficits, gait instability and memory loss in Cases 2 and 3. In fact, these symptoms strikingly resemble those described in the study by Renneboog *et al.* [30]. These authors suggested that

chronic hyponatraemia should no longer be considered an asymptomatic condition as is often suggested. Indeed, the neurologist of Case 2 had accepted chronic hyponatraemia as a side effect of carbamazepine, without advising fluid restriction. Because these subtle neurological symptoms in chronic hyponatraemia (unsteadiness, difficulty concentrating, reduced attention span, mild confusion, mild personality change) have just recently been clarified [30], it is conceivable that physicians ascribe these symptoms to the underlying disease or the patient's personality rather than to the—reversible—hyponatraemia per se. In the case of drug-induced SIADH (Cases 1 and 2)—and before the advent of vaptans—physicians had to weight the importance of treating the underlying disorder against the burden on the patient from the hyponatraemic side effects of the treatment. An interesting new example of this dilemma was recently described for imatinib, which was given for acute lymphoblastic leukaemia, but also induced SIADH [31].

If patients and physicians agree that the neurological symptoms—albeit subtle—of chronic hyponatraemia are too important to ignore, this means that monitoring and treatment of hyponatraemia should be given consideration. As reviewed in this supplement, several treatment options are available, each with their specific advantages and disadvantages. A role for the new selective vasopressin V2-receptor antagonists in these clinical examples is not difficult to imagine. In Cases 1 and 2, a vaptan would have enabled the patients to benefit from the drugs without hyponatraemia as a side effect. This is even more evident in Case 3. In him, current treatments failed to correct a chronic SIADH with hyponatraemia. Treating the side effects of one drug with yet another drug may not be the most elegant way of practicing medicine. However, in specific cases it may still prove the best approach for both patient and physician.

If vasopressin-receptor antagonists are used, the next question is for how long. This is especially important for transient causes of SIADH. When the stimulus for inappropriate vasopressin release fades, *hyper*natraemia lies in wait, although an intact thirst mechanism and access to water should prevent this. A practical approach could be to discontinue the vasopressin-receptor antagonist for 3–4 days at given intervals (maybe every 4–6 weeks), to evaluate whether hyponatraemia recurs or not. In hospitalized patients, transient SIADH may be common and vasopressin-receptor antagonists may help here to shorten the hospital stay. Although rare in the clinical trials, the risk of overly rapid correction of chronic hyponatraemia remains a concern, because it may lead to the osmotic demyelination syndrome. If overly rapid correction of chronic hyponatraemia does occur, infusion of dextrose 5% in water and perhaps even administration of dDAVP may be necessary to bring the serum sodium down to the desired level as a prophylaxis against permanent brain damage [32]. Taken together, the introduction of the vaptans is an interesting addition—if applied in the right circumstances—to the current armamentarium for hyponatraemia, and may give the patient more comfort and the physician a better therapy for hyponatraemia secondary to SIADH. We are now at the doorway to an entirely new treatment area and cannot be certain of what lays beyond. How useful will it really turn out to be? How many more patients with hyponatraemia shall we discover once the therapeutic progress opens our minds to hyponatraemia—'How many fish will be in the pond?' We just don't know. But then that's part of the fun—things may get better.

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