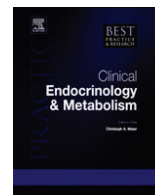




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Perspectives on the management of hyponatraemia secondary to SIADH across Europe

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The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is the most common cause of euvoelaemic hyponatraemia. However, although first described over 50 years ago, the management of hyponatraemia secondary to SIADH is not always straightforward. Some of the issues surrounding the management of hyponatraemia secondary to SIADH were explored in the European Hyponatraemia Survey completed by attendees of the European Hyponatraemia Network Academy Meeting 2011. This article describes the findings of this survey and the specific issues raised regarding the management of hyponatraemia secondary to SIADH in Europe. Some of these issues – including awareness, education, diagnosis, management and cost considerations of the condition – were common to countries across Europe.

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1. Introduction

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is the most frequent cause of euvoelaemic hyponatraemia.^{1,2} Despite being first described over 50 years ago,³ with essential and supplementary diagnostic criteria defined subsequently, clinicians may still face diagnostic obstacles

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when managing patients with this condition.^{4–6} A survey was conducted (the European Hyponatraemia Survey) to explore some of these obstacles among attendees of the first European Hyponatraemia Network Academy Meeting.

2. The European Hyponatraemia Survey

The European Hyponatraemia Survey was designed to explore issues surrounding the management of hyponatraemia secondary to SIADH across Europe with members of the European Hyponatraemia Network. Twenty delegates (10 nephrologists and 10 endocrinologists) completed the survey independently prior to the meeting. The survey was divided into the following four main sections:

1. Definition of hyponatraemia secondary to SIADH
2. Diagnosis of hyponatraemia secondary to SIADH
3. Management of hyponatraemia secondary to SIADH
4. Possible consequences of ineffectively treating hyponatraemia secondary to SIADH

2.1. Definition of hyponatraemia secondary to SIADH

All of the survey respondents recognised that hyponatraemia was a disorder of water balance and the majority agreed that vasopressin (also known as antidiuretic hormone) represented the humoral link between the brain and the kidney. Vasopressin is synthesised in the hypothalamus and released from the posterior pituitary into the bloodstream in response to increased serum osmolality or decreased serum volume. Following secretion, vasopressin circulates in the bloodstream to the kidneys, where it binds and activates the V_2 receptor.⁷ This stimulates an intracellular signalling cascade which leads to the insertion of the aquaporin-2 water channel proteins in the apical membrane and, ultimately, reduction of free water excretion and reabsorption of water.⁸

Measurement of urine osmolality and urine sodium concentration ($[Na^+]$) – which form part of the essential criteria for diagnosis of SIADH^{9,10} – were the most common (45% for each parameter) unprompted parameters selected by respondents when asked to identify biochemical tests essential for the diagnosis of hyponatraemia secondary to SIADH. Additional parameters used to define SIADH included euvoalaemia (35% of respondents), presence of low uric acid (15% of respondents) and low serum urea concentration (10% of respondents). Both low uric acid and low serum urea concentration are important supporting criteria for the diagnosis of SIADH and reflect the increased renal excretion of these solutes associated with SIADH.^{9,10}

2.2. Diagnosis of hyponatraemia secondary to SIADH

The majority of physicians (70% of respondents) reported using a set of biochemical parameters to diagnose hyponatraemia secondary to SIADH. Of these, the most common parameter for diagnosis was urine osmolality (93% of respondents). The majority of those surveyed (80% of respondents) believed that urine osmolality is not measured frequently enough. A number of respondents specified that they would require normal cortisol levels and thyroid function (both mentioned by 15% of respondents) prior to making a diagnosis of SIADH. As SIADH is a diagnosis of exclusion, failure to eliminate adrenal, thyroid and pituitary insufficiency could lead to a failure to recognise these important causes of hyponatraemia that require specific therapy.⁶

2.3. Management of hyponatraemia secondary to SIADH

Nearly all physicians (95% of respondents) recognised that acute hyponatraemia (of abrupt onset [<48 hours] and rapid progression) was the most important presentation of hyponatraemia necessitating an urgent intervention, in contrast to the less urgent 'non-acute' (2–10 days) or 'chronic' (of long duration [>48 hours] or frequent recurrence) hyponatraemia. The European Hyponatraemia Network members agreed that optimum treatment of 'non-acute' hyponatraemia was currently not well defined and that there was a need to further explore different treatment options in this setting.

Although it was believed that nephrologists and endocrinologists were best placed to manage hyponatraemia secondary to SIADH, respondents also felt that internal medicine specialists and intensive care specialists (35% and 15% of respondents, respectively) had a role to play.

No respondents believed that hyponatraemia secondary to SIADH was accurately managed. Although over 78% of respondents reported using fluid restriction to treat hyponatraemia secondary to SIADH, the majority (60%) were dissatisfied with its effectiveness. The reasons given for prescribing fluid restriction, despite this dissatisfaction, included:

- Lack of access to alternatives (38% of respondents)
- Fluid restriction was the standard first-line option (31% of respondents)
- Fluid restriction was cheap (25% of respondents)

Although sometimes effective, fluid restriction may be insufficient to correct hyponatraemia in patients with SIADH for several reasons. For instance, the patient may not be prescribed genuine fluid restriction and may instead have their fluid intake restricted to an arbitrary amount (i.e., 1 L/day). In cases where urine osmolality is high and a lot of water is being retained, this approach is unlikely to result in an increase in serum $[Na^+]$.¹¹ Moreover, patients may struggle to comply with fluid restriction and may drink out of social habit or thirst. Furthermore, fluid restriction may be complicated if there is a need to administer intravenous drugs and antibiotics as part of the patient's treatment.

The majority of respondents (90%) felt that hyponatraemia secondary to SIADH was more difficult to treat in certain patients, particularly those with an underlying tumour (identified by 50% of respondents as more difficult to treat). These patients were more likely to have chronic SIADH. A smaller number of respondents identified patients with acute, symptomatic SIADH, or those with acute, severe symptoms as more difficult to treat (identified by 33% and 22% of respondents, respectively).

2.4. Possible consequences of ineffectively treating hyponatraemia secondary to SIADH

When asked to list the consequences of not effectively treating hyponatraemia secondary to SIADH, the majority of respondents (95%) agreed that this would lead to neurological consequences. Only 10% of respondents thought it would increase morbidity while 20% believed it would increase mortality. Other potential consequences of leaving hyponatraemia untreated which were cited included; falls (30% of respondents), gait disturbances (15% of respondents), unsteadiness (10% of respondents), fractures (20% of respondents), reduced sense of well-being (15% of respondents) and cramps (5% of respondents).

All respondents agreed that not effectively treating hyponatraemia secondary to SIADH increased hospital stay. Interestingly, there was a divide between nephrologists and endocrinologists when specifically asked whether not effectively treating hyponatraemia secondary to SIADH had an impact on mortality. All endocrinologists that responded believed that not effectively treating hyponatraemia secondary to SIADH had an impact on mortality compared with only 50% of nephrologists.

3. Issues surrounding the management of hyponatraemia secondary to SIADH in Europe

All clinicians at the European Hyponatraemia Network Academy Meeting reported issues with the current management of hyponatraemia and SIADH specific to their country. However, during this discussion, some common issues regarding the management of hyponatraemia secondary to SIADH emerged.

3.1. Awareness and education

Hyponatraemia was not felt to be a priority among clinicians, and there was a lack of awareness of the implications of this condition on patient outcomes, particularly when hospital-acquired and mild-to-moderate in severity (125–135 mmol/L). Furthermore, the members of the European Hyponatraemia Network believed that hyponatraemia was likely to be ignored as it was perceived as complicated to diagnose and treat.

There was therefore a particular need to promote awareness and understanding of hyponatraemia in the emergency room and in specialities other than endocrinology and nephrology, because training

on electrolyte disorders for junior doctors was less rigorous. In addition, raising the awareness of hyponatraemia among nurses and patients could help ensure that treatment for hyponatraemia secondary to SIADH (such as fluid restriction) was adhered to.

Additional studies investigating the use of active treatment of hyponatraemia on length of hospital stay, symptom improvement and patient quality of life are underway. The publication of these studies will no doubt help increase awareness of this common condition and highlight the fact that it can be effectively managed.

3.2. *Diagnosis and management*

During the assessment of patients with hyponatraemia, volume status is not always correctly determined. It is essential to ensure that euvoalaemia and hypovolaemia are correctly distinguished during clinical assessment. It may therefore be beneficial to redefine the traditional classification system of hyponatraemia to take effective circulating blood volume into account, or to educate clinicians on the classification and differential diagnosis of hyponatraemia and promote understanding of intra- and extra-cellular fluid volumes in patients with dysnatraemias. Because the clinical assessment of the extracellular fluid volume is not very sensitive nor specific,¹² the assessment of volume status should not be used as the first and most important determinant to differentiate hyponatraemia.¹³

Accurate diagnosis of SIADH may be complicated by a lack of access to the necessary diagnostic tools, particularly urine osmolality. Some clinicians noted that this difficulty could be overcome by using alternative methods of estimating urine osmolality (e.g., urine specific gravity) when direct assessment was unavailable. Obstacles to the appropriate management of hyponatraemic patients could also be compounded as a result of patients moving quickly through the hospital system.

3.3. *Cost considerations*

Feedback from several countries suggested that treatment of patients with the recently available vasopressin receptor antagonists, such as tolvaptan, was likely to be restricted on the basis of cost. In order to overcome this restriction, there was a need to convey the importance of treating hyponatraemia secondary to SIADH to budget holders (for example, hospital managers and pharmacists) who might not necessarily be familiar with the condition. Communication of the impact of active treatment on patient prognosis and the benefits in the hospital setting in terms of a reduction in hospital stay was likely to help. For example, hyponatraemia was associated with increased morbidity,¹⁴ mortality^{15,16} and length of hospital stay,¹⁵ and mild hyponatraemia was associated with falls, attention deficits¹⁷ and fracture occurrence.^{18,19}

Unlike some conventional treatments, the efficacy of tolvaptan has been confirmed in two randomised, controlled trials: the SALT-1 and SALT-2 trials. In these trials, active treatment with tolvaptan was reported to improve patients' health status as assessed using the 12-item short form survey (SF-12 survey).^{20,21} Upcoming randomised trial data on the efficacy and safety of tolvaptan compared to conventional therapy with fluid restriction will help further define the role of this agent in the management of patients with hyponatraemia secondary to SIADH.

Clinical trials usually operate in an idealised environment and only assess efficacy in a limited population of patients. As a result, data from sources such as retrospective records, routinely collected databases and registries can provide valuable information about epidemiology and cost insights from a real-life setting.²² The Hyponatremia Registry is a prospective registry examining the comparative effectiveness of available treatments for hyponatraemia and their impact on resource utilisation in a real-world setting.²³ The objective of this registry is to obtain information about the demographics and clinical characteristics of patients who are being managed for euvoalaemic or hypervolaemic hyponatraemia in the hospital setting. The registry will also collect data on the comparative effectiveness of available treatments for the management of euvoalaemic and hypervolaemic hyponatraemia in the hospital setting, and to define and compare resource utilisation associated with management. Resource utilisation will be assessed in terms of medically necessary length of hospital stay and duration in the intensive care unit.²³

All of the tools mentioned above will be useful when conducting economic evaluation within a healthcare setting. It is important to take into account the national context, as systems for

reimbursement and evaluation may vary from country to country. For physicians communicating with local decision makers (i.e., those at a regional level) it is important to build credible arguments, which are evidence-based and relevant to the payor or purchaser being addressed. Ideally, these should include explanations of the burden of disease and the benefit of treatment in terms of morbidity, mortality, length of hospital stay and potential impact on budget.

4. Summary

Ineffective management of hyponatraemia can negatively impact patient prognosis. However, across Europe clinicians may face obstacles when managing hyponatraemia secondary to SIADH, many of which appear to be common throughout Europe. A lack of education and awareness regarding hyponatraemia was identified as the predominant barrier to the management of hyponatraemia secondary to SIADH by clinicians across Europe. In many regions, problems in clinically differentiating between hypovolaemic and euvolaemic patients was cited as an obstacle preventing accurate diagnosis. Initiatives, such as that undertaken by the European Hyponatraemia Network, could therefore play a critical role in advancing knowledge throughout Europe about this potentially serious condition. Finally, continuing research in the form of prospective, randomised trials and the Hyponatraemia Registry will help provide the additional data to address cost considerations in the management of hyponatraemia in a real-world setting.

Practice points

- The majority of clinicians diagnose hyponatraemia secondary to SIADH using a set of biochemical parameters.
- Experts in hyponatraemia believe that urine osmolality is not measured frequently enough in clinical practice.
- Although most physicians use fluid restriction to treat hyponatraemia secondary to SIADH, the majority are dissatisfied with its effectiveness.

Research agenda

- Ongoing research is needed to confirm that treatment of hyponatraemia reduces length of hospital stay, improves symptoms and improves patient quality of life.
- Ongoing research exploring treatment options in patients with hyponatraemia of 2–10 days duration will help to define optimum treatment strategies for this group of patients.
- In order to demonstrate the cost benefits of active treatments in patients with hyponatraemia secondary to SIADH, there is a need for data collected from a real-world setting such as that being conducted by The Hyponatraemia Registry.

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6. Conflict of interest

Dr. Hoorn has received consulting fees from Otsuka Pharmaceutical. Prof. Bouloux has been the recipient of honoraria for lecturing from Otsuka Pharmaceutical. Dr. Burst has received honorarium for oral presentations on hyponatraemia by Otsuka Pharmaceutical.

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