

FOREWORD

Hyponatraemia: new associations and new treatments

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Introduction

Hyponatraemia is the commonest electrolyte abnormality in clinical practice, and is the biochemical manifestation of a huge variety of illnesses. It is a common complication of malignancy, neurosurgical conditions, cardiac, liver and renal failure and pulmonary disorders. It is a side effect of many drugs and a frequent finding in the elderly, particularly those in long-stay institutions. Perhaps, because of the fact that hyponatraemia is a complication of so many disparate disorders, it has not traditionally fitted easily into the aegis of a single 'ology'; endocrinologists, renal physicians, geriatricians and internists may all assume responsibility for the diagnosis and treatment of hyponatraemia, according to the profile of the hospital and the clinical interests of the specialists which they employ. In some hospitals, there is no designated specialist who takes an interest in hyponatraemia. The evidence in the literature suggests that hyponatraemia is not only suboptimally investigated, but also poorly managed. The explanation is probably multifactorial – lack of dedicated specialists with an interest in hyponatraemia, poor awareness of investigative protocols and failure to recognise that hyponatraemia contributes to morbidity and mortality – but also that it is perceived that effective treatment is not available.

In this supplement, we have reviewed the evidence which suggests that hyponatraemia is associated with significant morbidity. In addition, new complications of mild hyponatraemia are being recognised which challenge the prevalent opinion that mild to moderate hyponatraemia does not require treatment, other than that directed to the underlying causative illness. We further discuss the potential role for the vaptans, the new aquaretic vasopressin antagonists, in the management of euvolemic hyponatraemia.

Epidemiology of hyponatraemia

Hyponatraemia occurs in 15–30% of hospitalised patients (1, 2). Hyponatraemia is particularly common in patients with neurosurgical conditions (3), intensive

care patients (4), nursing home residents (5) and the ambulatory elderly (6, 7). The commonest cause of hyponatraemia is the syndrome of inappropriate antidiuretic hormone (SIADH) (8). This syndrome was first described by Bartter & Schwartz (9), who described the characteristic pattern of abnormalities including hyponatraemia, clinical euvoemia, evidence of inappropriate concentration of urine and natriuresis. It commonly causes hyponatraemia in general medical inpatients (10, 11), and is the commonest cause of hyponatraemia in neurosurgical patients (3, 12). There are a number of clinical algorithms available to aid the clinician to distinguish SIADH from other forms of hyponatraemia, and the accurate identification of the cause of hyponatraemia is the key to successful treatment.

Morbidity of hyponatraemia

The neurological effects of low plasma sodium concentration are related to the severity of hyponatraemia and the rate at which the plasma sodium falls. Mild hyponatraemia (130–135 mmol/l) has traditionally been regarded to be asymptomatic, with nausea, headaches and anorexia occurring at moderate hyponatraemia (125–130 mmol/l) and more severe hyponatraemia (<125 mmol/l) associated with confusion, coma, seizures or even death. However, the classic publication of Arieff and colleagues (13) demonstrated clearly that symptoms can occasionally occur at higher plasma sodium concentrations, with severe hyponatraemia sometimes producing no perceived ill effects. Symptoms are well recognised to occur at higher plasma sodium concentrations when the rate of fall is rapid, whereas chronic hyponatraemia is associated with cerebral adaptation and relatively few symptoms.

New data which will be described in this supplement have shown that mild hyponatraemia causes gait disturbances, which are corrected with reversal of hyponatraemia (14). The gait abnormalities are not benign, as they are associated with an increased risk of falls. Furthermore, mild hyponatraemia seems to predispose to fractures in the ambulatory elderly (15). Part of the explanation for the increased risk of fracture in hyponatraemic patients when compared with normonatraemic patients may be the effect of hyponatraemia on bone mass. In an elegant series of studies in

This paper forms part of a supplementary issue of *European Journal of Endocrinology*. Otsuka Pharmaceutical Europe Ltd. has supported the publication of this supplement.

a well-established rat model of SIADH, Verbalis and colleagues have recently shown that hyponatraemic animals have marked reduction in femoral cortical and trabecular bone when compared with normonatraemic controls (16). The authors hypothesized that hyponatraemia predisposed to osteoporosis, a theory which they supported by reporting human data from the NHANES III study, which demonstrated that even in mild hyponatraemia (mean plasma sodium concentration 133 mmol/l), in patients over the age of 50 years, there was a linear association between femoral neck bone mineral density and serum sodium, with a reduction in total hip bone mineral density of 0.037 g/cm² for every 1 mmol/l drop in plasma sodium concentration. Plasma sodium concentration was calculated to explain 14.7% of the variation in total hip bone mineral density. These exciting new data contribute to a hypothesis which suggests that hyponatraemia predisposes to fractures not just by producing gait disturbances and increased likelihood of falls, but also by directly reducing bone mineral density to render the bones more vulnerable to fracture on impact. It is likely that investigation and testing of this hypothesis will generate further data in the near future.

Mortality and hyponatraemia

Early data suggested that severe hyponatraemia considerably increased the mortality in hospitalised patients (10), and considerable data have accumulated since then which corroborate the high mortality of hyponatraemia but which also suggest that mild hyponatraemia increases mortality. Severe hyponatraemia (<125 mmol/l) has been reported to be associated with in-hospital mortality of between 23 and 50% according to the plasma sodium concentration at presentation (17), and also with increased mortality at 6-month follow-up (11). Hyponatraemia has also been associated with increased mortality in the elderly (18), in heart failure (19), in pneumonia (20) and in intensive care patients (21). A recent paper presented data from a large cohort of 98 000 patients prospectively studied with outcomes measured up to 5 years after discharge from hospital. The authors found that even mild hyponatraemia (<135 mmol/l) independently predicted mortality (22). The relationship between mortality and plasma sodium concentration was most pronounced in patients with cardiac disease and metastatic cancer, which does raise the possibility that the excess mortality was associated with the conditions responsible for hyponatraemia, but interestingly, resolution of hyponatraemia during hospitalisation reduced the associated mortality, suggesting that the electrolyte disturbance was in itself a contributor to excess mortality. The results of this study were complemented by those of a population-based study from Denmark, which showed that

mild hyponatraemia (<137 mmol/l) also conferred increased hazard ratio for adverse outcome, even in the group with plasma sodium concentrations between 134 and 137 mmol/l (23). The overwhelming message from the published data is that even mild hyponatraemia increases mortality.

Medical costs of hyponatraemia

In the current economic climate, where bed occupancy is of major importance to hospital governance, data from several studies have shown that hyponatraemia is associated with increased length of hospital stay (3, 12, 17). In addition, data from a US healthcare database showed that in over 160 000 patients, hyponatraemia was a significant independent predictor of medical costs at 6 months (41% increase) and 1 year (46% increase) of follow-up (24). The data could not comment on whether treatment of hyponatraemia would lower medical costs. However, data available from both the US (22) and Europe (25) show that mortality is reduced by effective treatment of hyponatraemia.

Treatment options for hyponatraemia

Some of the therapeutic nihilism exhibited by the medical profession towards the treatment of hyponatraemia may reflect the lack of a specific treatment for euvoalaemic hyponatraemia, the commonest cause of hospital hyponatraemia. The data from the SALT trials have demonstrated that the vasopressin V2 receptor antagonist tolvaptan is a well-tolerated, effective treatment for hyponatraemia due to SIADH (26). The granting of a European licence for tolvaptan for the treatment of adult patients with hyponatraemia secondary to SIADH has given clinicians the therapeutic tool to directly treat the cause of SIADH. The articles in this supplement will discuss the implications for medical practice of the new data on the morbidity, mortality and economic burden of hyponatraemia and the potential impact of the new class of vasopressin antagonists, the vaptans.

Declaration of interest

Prof. Thompson is a member of the Tolvaptan advisory board for Otsuka Pharmaceuticals. This paper forms part of a European Journal of Endocrinology supplement, supported by Otsuka Pharmaceutical Europe Ltd. The opinions or views expressed in this supplement are those of the authors, and do not necessarily reflect the opinions or recommendations of Otsuka Pharmaceutical Europe Ltd.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

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Received 16 April 2010

Accepted 19 April 2010