Syndrome of inappropriate antidiuresis should it be managed by specialised endocrinologists?

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The syndrome of inappropriate antidiuresis (SIAD) is the commonest cause of hyponatraemia in hospitalised patients, accounting for 43% of patients with a plasma sodium concentration of <130 mmol/l [1]. Although there are virtually no data on mortality in SIAD, mortality in all-cause hyponatraemia has been reported to be elevated in almost every paper on the subject [2–4]. Hyponatraemic patients are also vulnerable to morbidity related to falls [5], fractures [6] and osteoporosis [7]. In the absence of separate studies in SIAD, it is widely accepted that patients who have hyponatraemia due to SIAD are vulnerable to the same risk of the morbidities and mortality associated with all-cause hyponatraemia. This has prompted considerable interest in whether treatment of hyponatraemia can improve outcomes in SIAD.

Unfortunately, there is little data in the literature upon which to construct evidence based guidelines for the management of hyponatraemia due to SIAD. In the absence of a solid evidence base, there are controversial differences between the US recommendations [8] and the European guidelines [9] on treatment of SIAD. The US recommendations acknowledge that second-line treatment of SIAD, after failure of water restriction can be vaptans, urea or frusemide with sodium chloride supplementation, whereas the European Guidelines specifically advise against vaptans. So where are the gaps in our knowledge in the literature? The mortality in SIAD separately from that due to all-cause hyponatraemia is not known. Mortality studies have

assessed the effects of hyponatraemia on death rate, without separating out the relative mortality of SIAD from other causes of hyponatraemia. In addition, as very few studies have firmly ascertained the full diagnostic criteria for SIAD in their study cohorts [10], the accuracy of data from many SIAD studies is questionable.

The situation is complicated by the lack of studies on the response of plasma sodium to established treatments for SIAD. There are no prospective randomised-controlled trials which have reported the effects of water restriction, and many second-line treatments, in SIAD. There is however firm data on the response of SIAD-related hyponatraemia to treatment with vaptans; the randomised, placebo-controlled SALT studies showed that a mixed population of patients with SIAD and hypervolaemic hyponatraemia demonstrated a larger rise in plasma sodium concentration in response to tolvaptan than to placebo [11], and a later subgroup analysis confirmed that similar biochemical responses were consistent in the SIAD subgroup [12]. However, we still await the results of trials which compare the proven benefits of vaptans with first-line treatment with water restriction.

It is therefore timely to see the results of an intervention study in SIAD patients in this journal [13]; the paper reported the effects of specialised endocrine care on outcomes in SIAD. The authors have a proven track record in the field, and as a group who have highlighted the poor ascertainment of basic diagnostic criteria for SIAD in clinical practice [10], they have unsurprisingly defined their SIAD cohort rigorously, and we are comfortable that they have excluded adrenal insufficiency. They have compared the effect of general care of SIAD—which included some patients who had the benefit of endocrine consultation—with those managed entirely by endocrine input. The two

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groups were not randomised, which the authors have defended on the grounds that it would not have been ethical to prohibit consultation with endocrinology services in the group assigned to no active specialist care.

Both study groups were small, and as the 'routine care' group also contained patients who had received endocrine input, it would have been reasonable to predict that it would be impossible, because of insufficient power and a mixed control group, to demonstrate improved outcome in the group who received active endocrine care. Instead, the group who received specialised care attained the primary end-point of a rise in plasma sodium of >5 mmol/l in half the time it took those in the 'routine' group (3.5 vs. 7 days). Furthermore, this biochemical improvement was associated with an unquantified improvement in neurological symptoms and a mean reduction in hospital stay of almost 4 days, which neatly equated to the time difference in the rate of correction of plasma sodium to the primary end-point. More surprising still, endocrine input was associated with a statistically significant decrease in in-hospital mortality (5 vs. 17%). Finally, plasma sodium concentration was less likely to be <130 mmol/l in the group with endocrine input (6 vs. 42%), even though they were discharged earlier. These are very positive effects.

What do we derive from this data? Firstly, it should be acknowledged that it is genuinely difficult to conduct randomised trials into the outcomes of treatment of hyponatraemia. The authors have conceded that a randomised trial would be preferable, but defended their decision not to randomise on the grounds that a randomised design would have prohibited expert input for difficult cases in the group randomised to 'routine care'. With the relative weakness of the study design acknowledged however, the results have impressively shown that specialised input for SIAD, from an endocrine unit with undoubted expertise in managing hyponatraemia, produces clear benefits over non-specialised care. Their data shows that target elevation for plasma sodium concentration was achieved more quickly, and patients were discharged more rapidly from hospital, with a lower mortality.

What we cannot judge, however, is what the cause for the different outcomes were. The improved outcomes in the intervention group are likely to be multifactorial; they had more changes in therapy and had a higher rate of application of water restriction. It is likely that a more active management of hyponatraemia by experts in the field had more impact than the implementation of water restriction. The authors cite the lack of impact of water restriction in the observational setting of the hyponatraemia registry [14], and in routine clinical practice [15–18], but perhaps in the setting of a small intervention trial, their efforts and expertise produced more effective implementation of water restriction. In addition, the range of secondary interventions

used was very varied, so remain in the position that we are unclear what the most effective intervention—water restriction, vaptans or saline infusion—was.

Can the results of the paper be reproduced in clinical practice? Without an analysis of what the most effective aspect of the intervention was, it is hard to know how the results could be replicated. In addition, as the expertise of the authors of the paper is well developed, it is unclear whether the results could be reproduced in routine clinical practice, when non-specialists manage hyponatraemia, or where there is less vested interest than there is in the context of a clinical trial where the outcomes determine the likelihood of journal publication. The authors acknowledge this point. They stress the need for hospital specialists, whether they be endocrinologists or nephrologists, to be involved in the active management of hyponatraemia, particularly if it is severe or symptomatic, recommendations which we would endorse.

The authors should be commended for their efforts. Perhaps the most salient point they emphasise is that their data raises as many questions as it answers. The need for genuine randomised controlled trials comparing the effects of different treatments is crucial. Although the authors used water deprivation as first-line, in line with all recommendations [8, 9, 18], there is no randomised control trial data to indicate that this treatment modality influences outcomes, or even reliably increases plasma sodium concentration. The authors could not attribute the success of their intervention to any specific therapy as they used multiple therapies, in a non-randomised way, and without consistency in dose or length of treatment. It is impossible therefore to conclude which is the best intervention to achieve clinical goals. The conclusion of this editorial is therefore the same as that of the paper; the results are of interest and almost certainly a positive reflection of their own efforts and intervention, but multicentre, prospective, randomised controlled trials are needed to guide us in our management of SIAD. Their results do suggest that SIAD should be managed by experts, though whether the experts should be endocrinologists, or other specialities such as nephrology, remains a reflection of local interests and human resources.

Compliance with ethical standards

Conflict of interest Professor Thompson has received honoraria for lectures from Otsuka Pharmaceuticals. There are no other funding conflicts for either of the authors.

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