

## ORIGINAL ARTICLE

## Investigation and management of severe hyponatraemia in a hospital setting

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**Aims:** To evaluate the assessment and management of severe hyponatraemia in a large teaching hospital.  
**Methods:** Inpatients with serum sodium  $<125$  mmol/l were identified prospectively from a laboratory database over a six month period. Notes were examined and data extracted. Case notes were carefully reviewed retrospectively by a consultant endocrinologist with regard to accuracy of the diagnosis and the appropriateness of investigations and management.

**Results:** 104 patients with a serum sodium  $<125$  mmol/l were identified. Mean (SD) age was 69 (14), 52% were female, mean hospital stay was 16 (12) days, and overall mortality 27%. Adequate investigations were rarely performed. Only 28 (26%) had plasma osmolality measured, 29 (27%) urine osmolality, 11 (10%) urinary sodium, 8 (8%) plasma cortisol, and 2 (2%) a short Synacthen test. Comparing the "ward" and "specialist review" diagnoses, there were significant discrepancies for "no cause found" (49% v 27%,  $p<0.001$ ), alcohol (6% v 11%  $p<0.01$ ), and syndrome of inappropriate antidiuresis (20% v 32%,  $p=0.001$ ). Treatment was often illogical with significant management errors in 33%. These included fluid restriction and intravenous saline given together (4%) and fluid restriction in diuretic induced hyponatraemia (6%). Mortality was higher in the group with management errors (41% v 20%  $p=0.002$ ).

**Conclusion:** Severe hyponatraemia is a serious condition, but its investigation and evaluation is often inadequate. Some treatment patterns seem to be arbitrary and illogical, and are associated with higher mortality.

Hyponatraemia is the most common electrolyte disturbance encountered in clinical practice, with a prevalence up to 15% in a general hospital population.<sup>1,2</sup> It is associated with considerable morbidity and mortality, but with differing views on optimal management.<sup>3</sup> The evaluation of hyponatraemia can be challenging. Clinical judgment and laboratory investigations are important to help elucidate a diagnosis. Two recent studies have looked specifically at the investigation and management of hyponatraemia in a hospital setting.<sup>4,5</sup> Both studies examined populations with severe hyponatraemia (plasma sodium  $\leq 120$  mmol/l) and concluded that investigations were often inadequate. Both reports however, involved small numbers of patients (47 and 42 patients respectively). In a separate report, Hochman *et al* looked at a population with less severe hyponatraemia (plasma sodium  $\leq 130$  mmol/l) and commented on aetiology, treatment, and prognosis. They found a high mortality rate (30%) and concluded that this was secondary to the underlying medical condition, rather than the degree of hyponatraemia or the subsequent treatment.<sup>6</sup>

None of these studies addressed the accuracy of the diagnoses reached, or whether management was clinically appropriate. Also, the question of whether inappropriate management of hyponatraemia is correlated with adverse outcome, has not been reported.

We have therefore studied a large cohort of patients to assess the accuracy of diagnosis and appropriateness of investigations and management. Whether inappropriate management affected clinical outcome was also assessed.

## METHODS

## Patient selection

The study was conducted in a large teaching hospital (University Hospital Aintree) with approximately 900 beds. The hospital includes all major specialties except for

paediatrics and cardiothoracic surgery. All inpatients who had renal function tests and electrolytes (serum sodium, potassium, urea, and creatinine) requested over a six month time period, were identified from a computer based laboratory database. Those patients with a serum sodium concentration of equal or less than 125 mmol/l at any point during the admission, were selected. Serum sodium was measured using indirect ion selective electrodes with either Advia 1650 (Bayer) or Konelab 60i (Labmedics) analysers.

## Data collection

Hospital case notes were examined for each patient and clinical and demographic details, final diagnosis, investigations and management were recorded. Details were entered onto a standard data collection sheet and later transferred to a Microsoft Excel spreadsheet. Each case was then individually reviewed by a consultant endocrinologist (GVG) with an interest in hyponatraemia. If appropriate, based on the clinical and investigative information available, an alternative diagnosis was made (or a "no diagnosis possible" option chosen) if it was felt appropriate. Management given was similarly examined as to its appropriateness or otherwise.

## Standard setting

To judge clinical performance, we attempted to set pre-determined standards for investigation, diagnosis, and management. We considered that minimum ideal set of investigations for severe hyponatraemia would be plasma sodium, creatinine, and osmolality; urine osmolality and sodium, and assessment of adrenal function preferably by short Synacthen test. Standards for the major diagnostic criteria of hyponatraemia were as follows:

- Syndrome of inappropriate antidiuresis (SIAD). We used the original criteria of Bartter and Schwartz<sup>7</sup>—that is,

**Table 1** Causes of hyponatraemia, by initial and retrospective diagnosis

Cause	Hospital diagnosis n (%)	Retrospective diagnosis n (%)	Odds ratio	p Value
No cause found	51 (49)	28 (27)	2.61	<0.001
Thiazide diuretics	14 (13)	19 (18)	0.70	0.15
Other diuretics	8 (8)	8 (8)	1.00	1.00
Alcohol related	6 (6)	12 (11)	0.47	0.01
SIAD	21 (20)	34 (32)	0.52	0.001
Primary polydipsia	1 (1)	0 (0)	3.02	0.41
"Drip arm"*	1 (1)	1 (1)	1.00	1.00
Dextrose infusion	1 (1)	3 (3)	0.33	0.04
Addison's disease	0 (0) †	1 (1)	0.3	0.16
Renal failure	2 (2)	1 (1)	2.02	0.48
Heart failure	0 (0)	1 (1)	0.3	0.16
Post-TURP	0 (0)	1 (1)	0.3	0.16
Hypothyroidism	1(1)	1(1)	1.00	1.00

SIAD syndrome of inappropriate antidiuresis; TURP, trans-urethral prostatectomy; \*Spurious result secondary to taking blood proximal to an intravenous infusion site. †When values of "0" are present 0.5 is added to all of the figures so as to allow an odds ratio and p value to be calculated.

hyponatraemia and hypo-osmolality, inappropriately raised urine osmolality and natriuresis, absence of clinical hypovolaemia, and normal renal and adrenal function. In the context of notes review, however, it was rarely possible to ascertain volaemic status, and adrenal function was rarely tested for. A presumptive diagnosis of SIAD was therefore often made without these criteria.

- Diuretic induced. This was diagnosed when hyponatraemia was associated with diuretic treatment (particularly thiazides) and there was no other likely cause.
- Alcohol related. This was considered the probable cause when patients with severe hyponatraemia had significant alcohol related liver disease, and no other obvious cause for the hyponatraemia.
- Infusion related. Hyponatraemia related to dextrose infusions was diagnosed when excessive amounts of intravenous dextrose had been used. This was usually in postoperative patients or diabetic patients on glucose-potassium-insulin (GKI) infusions. There was no other cause, and preferably hypo-osmolar urine was present.

Management errors were considered present when hyponatraemia was iatrogenic or when intravenous NaCl treatment was given in inappropriate or potentially dangerous situations. It was also requested that if fluid restriction was used in SIAD, volumes below 1.5 litres/day would be advised. Probable drug causes of hyponatraemia were expected to be stopped, or at least acknowledged (for example, thiazides). Failure to exclude hypoadrenalism in clinically suggestive scenarios was also considered a management error.

### Statistical analysis

Data were analysed using the Microsoft Excel statistical program and Stats Direct software. Continuous variables were expressed as mean (1 SD) and compared with unpaired Student's *t* tests. Categorical variables were expressed as

percentages and compared with the  $\chi^2$  test. Two tailed p values were considered significant when  $p < 0.05$ .

### RESULTS

Over the six month period 104 patients were identified using the above criteria. All case notes were complete and available.

#### Baseline characteristics

The mean age of the patients was 69 (SD 14) years (range 33–95) and 52% were female. Serum sodium was recorded as the lowest value during the admission (mean 120 (SD 4) mmol/l). Inpatient mortality was 27% (28 of 104).

#### Diagnosis

Table 1 shows the hospital diagnoses and the later retrospective diagnoses. It can be seen that after review there was a significant reduction in "no diagnosis" cases, from 49% to 27% ( $p < 0.001$ ), made up by increases in diagnoses of alcohol related causes, SIAD often of undetermined origin, and secondary to dextrose infusions. Overall, in 44 cases (42%), the inpatient diagnosis was regarded as inconsistent with the clinical and investigative details available.

#### Investigations

Table 2 shows the investigations recorded in the case notes. By definition, all patients had serum (sodium) levels measured. However, serum and urine osmolality was recorded in only the minority of cases (26% and 27% respectively) while only 10% had urine sodium test performed. Hypoadrenalism was rarely excluded—a random plasma cortisol was done in 8% and a Synacthen test in 2%.

#### Treatment

Table 3 shows the treatments given to the patients. No specific treatment was given in 42% of cases, with fluid restriction (36%) and intravenous saline (23%) being the next most frequent managements. Surprisingly, in 7% of cases both fluid restriction and intravenous saline were given.

#### Management errors

These were specific cases, where after careful deliberation, management was thought to be inappropriate or inadequate and are summarised in table 4. There were 10 cases where investigations were not done that could have significantly changed management and possibly, outcome. Of these, seven did not have hypoadrenalism considered, although six cases had widespread abdominal malignancy and the possibility of adrenal metastases seemed to have been overlooked. One further case had a classic clinical presentation of Addison's

**Table 2** Investigations performed on patients

Investigation	n (%)
Serum sodium	104 (100)
Serum creatinine	102 (96)
Urine osmolality	29 (27)
Serum osmolality	28 (26)
Urine sodium	11(10)
Plasma cortisol	8 (8)
Short Synacthen test	2 (2)

**Table 3** Treatments given for hyponatraemic patients

Treatment	n (%)		
No treatment	44 (42)		
Fluid restriction	38(36)	1 l/day	20 (19)
		1.5 l/day	15 (14)
		0.5 l/day	3 (3)
Intravenous saline	24 (23)		
	0.9%		
	1.8% (with 4% dextrose)		1 (1)
Fluid restriction and intravenous saline	7 (7)		
Democlocycline	1 (1)		
DDAVP	1 (1)		
Diuretic stopped/reduced	10 (10)		
Dextrose changed to saline	2 (2)		

DDAVP, desmopressin.

disease. Worryingly, 6% of patients were diagnosed with diuretic induced hyponatraemia and yet still fluid restricted. Other inappropriate treatments included “blind” intravenous saline treatment in non-critical situations, and intravenous saline in heart failure. There were four (4%) clearly iatrogenic cases of hyponatraemia—three due to over-infusion of dextrose fluids, and one post-TURP (trans-urethral prostatectomy).

### Mortality and management

Overall, there were 34 cases (33%) considered to have significant management errors. Out of these, 14 patients died (41%). The cohort that was felt to be managed appropriately, however had a mortality of 14 of 70 (20%). The excess in the inappropriately managed group was significant ( $p=0.002$  OR 2.8 (95%CI 1.02 to 7.55)). Only 26% of the cases managed inappropriately reached a final plasma sodium in the normotraemic range (135–145 mmol/l), compared with 40% of the appropriately managed cohort ( $p=0.17$ ). There was no significant difference in mean inpatient stay between the two groups.

### DISCUSSION

This is one of the few studies examining the detailed practical aspects of diagnosis, investigation, and management of hyponatraemia, in a hospital setting. Our population had a mean age of 69 years with an inpatient mortality of 27%. Comparison with other studies is hampered by the use of different cut off values of plasma sodium, but most studies have found mortality rates between 30% to 50%.<sup>4-6</sup> Others

### Learning points

- Documentation of diagnosis in hyponatraemia should be clear; volume status and accurate fluid balance should be recorded.
- Investigations should include urea, creatinine, electrolytes, plasma and urinary osmolality, and urine sodium.
- Attention should be given to diuretic therapy, particularly thiazides, when interpreting urine sodium and osmolality in the setting of SIAD.
- Adrenal metastases in intra-abdominal malignancy causing hypoadrenalism should not be overlooked.
- Management should be carefully thought out with adequate investigation; it is often appropriate to treat the underlying cause only.

have also reported the high use of diuretics (particularly thiazides) being found in patients with hyponatraemia.<sup>8</sup> A potential weakness of our study is that data were based on recordings in the patient’s notes. It may have been that some investigations and treatments were not recorded. Performance could therefore possibly have been better than we have measured; although it may also have been worse.

A strikingly large number of cases (49%) had no diagnosis made, although when the notes were examined by an endocrinologist this was reduced to 27% (see table 1). We accept that this is a subjective reassessment, but the difference is nevertheless striking. Endocrine review attributed more cases to alcohol related disorders and SIAD than during the original admission. The latter is interesting as SIAD is traditionally thought to be over-diagnosed.<sup>9</sup>

Diagnostic difficulties were perhaps not surprising, given the frequently inadequate nature of investigations (table 2). Only just over a quarter had full serum and urine osmolality studies, and adrenal status was assessed in only 10%, with only 2% having a short Synacthen test. The value of a random cortisol level is doubtful, and overall many cases of primary or secondary hypoadrenalism could have been missed. As well as missing cases of hypoadrenalism, these investigative shortfalls will have hampered the accurate diagnosis of SIAD.<sup>10</sup> It is salutary to realise that nearly 50 years after the delineation by Bartter and Schwartz of the diagnostic criteria, that poor investigation still leads to under-diagnosis of SIAD.<sup>7</sup> The minimal use of urine osmolality and sodium as measures of volaemia reflects a lack of consideration of the pathophysiology of dilutional hyponatraemia due to SIAD.

**Table 4** Management errors

Treatment	n (%)
Inadequate investigation, which could have changed management*	10 (10)
Diuretic induced hyponatraemia treated with fluid restriction	6 (6)
Treatment with fluid restriction plus intravenous saline	4 (4)
Thiazides continued when probably the cause of hyponatraemia	4 (4)
“Blind” intravenous saline for modest (>125 mmol/l) hyponatraemia in a non-critical situation	3 (3)
“Blind” 0.18% saline in severe (<125 mmol/l) hyponatraemia	1 (1)
IV saline in heart failure	1 (1)
DDAVP used in SIAD	1 (1)
iatrogenic causes secondary to:	
IV dextrose	3 (3)
Post-TURP	1 (1)

\*Seven of these cases did not have hypoadrenalism considered where it was clinically possible.

Treatment was variable and often arbitrary. Although a large number of patients had no active treatment (42%), this may have been appropriate, as management should be directed to the underlying cause.<sup>11</sup> Fluid restriction when used, however should ideally ensure a negative fluid balance of about 500 ml a day (for example, an intake of 1 litre/day or less).<sup>12</sup> This degree of fluid restriction was only achieved in 39% of patients treated in this fashion. Other management shortfalls included fluid restriction in diuretic induced hyponatraemia (6%), fluid restriction and intravenous saline used together (4%), and continuing thiazide diuretics when they were the probable cause of hyponatraemia (4%) (see table 4). We have included serious investigative omissions as management errors—these comprised a small group—in which a treatable diagnosis was not considered or tested for (for example, adrenal metastases with hypoadrenalism in patients with abdominal and/or disseminated malignancy).

The use of saline in hyponatraemia is subject to debate.<sup>5 13-15</sup> Some have advised hypertonic saline if hyponatraemia is severe (<120 mmol/l) or if the patient has symptoms of hyponatraemic encephalopathy.<sup>3</sup> We took this variation of clinical practice into account when assessing the use of intravenous saline in our patients. We did however find cases where isotonic saline was used completely arbitrarily, with little or no investigations carried out, and seemingly regardless of the patient's clinical status (table 4). The use of 4% dextrose/0.18% saline solution in one patient, who had a plasma sodium of 113 mmol/l was obscure as was the use of DDAVP in a patient thought to have SIAD (at best bizarre, and potentially dangerous). Overall, we found that 33% received illogical or erroneous treatment.

To our knowledge, the finding that patients who have been managed inappropriately in hyponatraemia having a higher mortality has not been reported in the literature. We do not assume that errors in management themselves were responsible for these deaths, as most patients were seriously ill and elderly, and a number had widespread malignancy. Nevertheless, it is equally possible that more appropriate management may have reduced the overall mortality rate. Interestingly, we also found a non-significant trend towards more efficient normalisation of serum sodium concentrations in the appropriately managed group (40% compared with 26% normalising their serum sodium during admission).

Our hospital is unlikely to be unique in finding inadequacies in the management in hyponatraemia. Other studies have certainly found a comparable lack of investigations, although have not looked at management and investigative

inadequacies in such detail, nor have they related management errors to adverse outcome.<sup>5 6 16</sup> Our results suggest an urgent need for the use of investigative protocols and perhaps management pathways in patients with significant hyponatraemia.

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