ORIGINAL ARTICLE

Hyponatraemia: Etiology, Management and Outcome

Aasima Yawar, Abdul Jabbar, Naeem-ul-Haque, Lubna M. Zuberi, Najmul Islam and Jaweed Akhtar

ABSTRACT

Objective: To determine the etiology of hyponatraemia, the treatment instituted and the outcome of treatment in a tertiary care hospital setting.

Study Design: Case series.

Place and Duration of Study: The Aga Khan University Hospital, Karachi, between January and June 2004.

Methodology: Case records of 220 patients admitted to the medical service were identified through computerized hospital patients' data. All patients ≥ 15 years with a sodium level on admission of ≤ 130 mmol/litre were included. The records of those patients were reviewed for relevant demographic, clinical and laboratory data, in addition to the diagnosis, treatment and outcome of hospitalization. The data was analyzed through SPSS software version 11.0.

Results: Over a 6-month period, 220 patients were admitted with hyponatraemia (serum sodium ≤ 130 mmol/L). Of those127 females and 93 males, the mean age was 65 ± 13.29 years. Neurological symptoms were the presenting feature in 25% patients. The mean serum sodium level on admission was 119.46 mmol/L. The rate of correction was >10 mmol/L/24 hours in 17% patients. The average duration of stay was 4 days. The mortality was 6.8%. Medicines accounted for 30% cases of hyponatraemia, of which diuretics, angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blockers (ARBs) were top of the list. Other causes were gastrointestinal in 25%, chest infection in 11% patients, depletional hyponatraemia in 10% patients, SIADH (Syndrome of Inappropriate Antidiuretic Hormone) in 6% patients, congestive cardiac failure and malignancy in 5% each and chronic liver disease in 3.6% patients.

Conclusion: Hyponatraemia was seen more commonly in the elderly, major causes being gastrointestinal losses and use of drugs. Serum sodium correction should be less than 10 mmol/L/24 hours. The treatment plan be directed to correction of the underlying cause. Diagnosis of SIADH should be sought with appropriate investigation.

Key words: *Hyponatraemia. SIADH. Mortality. Etiology. Drug-induced. Gastrointestinal loss. Neurological symptoms.*

INTRODUCTION

Hyponatraemia is one of the commonest biochemical abnormalities encountered in the general hospitalized population with an incidence of 1%.[1,2] Hyponatraemia is defined as serum sodium level of less than 135 mmol/L and severe hyponatraemia as level less than 120 mmol/L.[3] Hyponatraemia particularly in its milder forms may be a reflection of non-specific illness so it is also called the "biochemical ESR"[4] assuming importance due to the associated mortality and morbidity.[5,6] On the converse, many believe that the mortality and morbidity associated with hyponatraemia may be due to the associated cardiac, pulmonary, hepatic, neurological and renal conditions rather than the electrolyte imbalance alone and may actually reflect the severity of the primary illness.[5,7] Making an accurate diagnosis and instituting appropriate therapy, therefore, may be crucial.

Diabetes and Endocrinology Section, Department of Medicine, The Aga Khan University Hospital, Karachi.

***Correspondence:** Dr. Aasima Yawar, Flat 3H, Street 3, Askari-IV, Rashid Minhas Road, Karachi.*
E-mail: yawarazim@hotmail.com

Received January 9, 2006; accepted June 3, 2008.

Despite being one of the commonest electrolyte imbalances, there have been problems in both the management and treatment of this condition. Mild hyponatraemia may be asymptomatic, with presentation varying from confusion to hallucinations, agitation and coma. History and physical examination needs to be accompanied by relevant biochemical profile as the treatment given depends on the underlying cause. If hyponatraemia is inadequately investigated, the management instituted may actually be inappropriate and inadequate. Having all these factors in mind, the purpose of this study was to determine the aetiology, treatment and outcome of hyponatraemia in patients hospitalized at a tertiary care hospital during a certain period.

METHODOLOGY

It was a case series study, which included all adult patients ≥ 15 years admitted to the Aga Khan University Hospital, Karachi under the medical services from January to June 2004 with serum sodium level of ≤ 130 mmol/L on admission. Patients' records were reviewed for information such as age, gender, signs and symptoms related to hyponatraemia on admission, assessment of volume status (hypovolaemic, euvolaemic or hypervolaemic) according to clinical assessment based on presence or absence of

tachycardia, postural hypotension, dry mucous membranes, peripheral oedema, raised JVP, pulmonary oedema, ascites and substantiated with determination of blood urea and serum creatinine values. Serum sodium (Na) levels were noted on admission and at 24 and 48 hours. Final Na level (which may be last Na level checked during admission or Na prior to discharge) was also noted. Simultaneous plasma glucose was also noted and sodium levels were corrected accordingly if glucose levels were >100 mg/dl. The formula used for correction was 1.5 mmol/L increment in sodium level for each 90 mg/gl[1] rise in glucose above 100 mg/l. Serum potassium, chloride and bicarbonate levels were noted on admission. Urine and plasma (measured and calculated) osmolality, urinary spot sodium and urine specific gravity was noted wherever available. Similarly, a note of thyroid function tests, cortisol (random and/or after short Synacthen test), Liver Function Tests (LFTs) and lipid profile was made. Maintenance of fluid balance charts, treatment received, be it fluid restriction, intravenous fluids (with type of fluid) or a combination of both, with and without use of Oral Rehydration Solution (ORS) was noted. Other associated comorbid conditions, duration of stay and outcome were also noted. A sodium level of ≤ 120 mmol/L would be rechecked and reported to the ward.

Data was analysed by SPSS version 11. Values were expressed as mean ± standard deviation (SD). Significance was analysed by students t-test and p-values <0.05 were considered to be significant.

RESULTS

Over a 6-month period, 220 patients ≥ 15 years of age were admitted to the medical services with serum sodium on admission of ≤ 130 mmol/L. There were 127 females and 93 males. The mean age was 65 ± 13.29 years, which ranged from 15 to 98 years. The mean sodium on admission was 119.46 mmol/L with a range of 101 to 130 mmol/L. Over half (53%) patients were in the range of 120-130 mmol/L, 34.5% (76) were in the range of 110-119 mmol/L and smaller numbers (12%) were in the range of 100-109 mmol/L. Serum sodium was checked in 187 patients after 24 hours and 141 had their serum sodium checked after 48 hours as well. One hundred and sixteen patients had serum sodium checked beyond 48 hours. A quarter of patients presented with symptoms suggestive of cerebral oedema/cortical dysfunction. Of those, 61% had drowsiness, 35% had weakness and irritability was seen in 4%. However, it could not be ascertained whether the symptoms were due to hyponatraemia alone or due to other medical conditions. For those patients, serum sodium levels on admission were similar to the study group and 11% had serum sodium levels between 100-109 mmol/L.

Most of the patients (201) received intravenous (IV) fluids. Six patients were placed on fluid restriction alone and 132 on intravenous fluids alone. Sixty patients received intravenous fluids and had free fluid restriction. Six patients were on a combination of fluid restriction, IV fluids and ORS.[10] Patients received diuretics, while they were stopped in one patient. However, 3 patients received no treatment for their hyponatraemia.

Of the patients receiving intravenous fluids, 145 (66%) received normal saline followed by Ringers lactate solution given to 9 patients (4%), 3% saline to 3 patients and 0.45% saline was given to one patient. Dextrose and dextrose saline were given to 6% and 1.8% patients respectively.

The rate of correction was >10 mmol/L in 17% in the first 24 hours, however, it was 4.5% in the subsequent 24 hours. This has been summarized in Table I.

Table I: Rate of correction of hyponatraemia in the first 24 hours and the subsequent 48 hours.

Rate of correction	Initial 24 hours	Subsequent 48 hours
>15 mmol/L	17 (7.7%)	4 (1.8%)
10-15 mmol/L	21 (9.5%)	6 (2.7%)
5-10 mmol/L	63 (28.6%)	48 (21.8%)
0-5 mmol/L	59 (26.8%)	57 (25.9%)
No improvement	27 (12.3%)	26 (11.8%)

Of the patients who had a rate of correction of >10 mmol/L there were 4 mortalities. Three of those patients had initial sodium level between 110-120 mmol/L and one patient had serum sodium level of 125 mmol/L.

The duration of stay ranged from less than 24 hours to 27 days with mean of 4 days.

Mortality was seen in 15 (6.8%) patients. Mean duration of stay in the expired patients was 7.7 days. Four left against medical advice, one was shifted to another hospital and the rest were discharged home. Infection was the leading cause of mortality found in 7 (46%) patients, malignancy (40%) and cardiac and metabolic causes in 4% patients each.

In patients who did not survive, half had corrected serum sodium level on admission between 110-119 mmol/L, 2 had initial values between 100-109 mmol/L and 5 patients had serum sodium levels between 120-130 mmol/L.

Most patients had more than one cause for their hyponatraemia. Therefore, they were divided into major attributer and minor factor for hyponatraemia summarized in Table II.

Among the drug induced category of causes, almost one-third of those patients were on diuretics and another one third were on ACE inhibitors. ARBs, Selective Serotonin Release Inhibitors (SSRIs), carbamazepine and other anti-depressants were being caused in the rest.

Thyroid function tests were done in 104 patients. Adrenal axis was checked in 57 patients with a short

Table II: The major and minor causes of hyponatraemia in the studied group.

	Major cause (No./%)	Minor cause (No./%)
Medicines	66 (30%)	87 (40%)
Gastrointestinal loss	55 (25%)	3 (1.4%)
Chest infection	24 (11%)	6 (2.7%)
Depletional	22 (10%)	22 (10%)
SIADH	13 (6%)	-
Malignancy	11 (5%)	5 (2.3%)
Congestive cardiac failure	11 (5%)	1 (0.5%)
Chronic liver disease	8 (3.6%)	1 (0.5%)
Hypothyroidism	6 (2.7%)	-
Psychogenic polydipsia	5 (2.3%)	-
Panhypopituitarism	2 (0.9%)	-
Addison's disease	1 (0.5%)	-
Chronic renal failure	1 (0.5%)	1 (0.5%)
Unknown	4 (1.8%)	-

Synacthen test and or a random cortisol level. Spot sodium determination was done in 116 patients and urine osmolality was checked in 112 patients. LFTs were conducted in 109 and lipid profile was obtained in 19 patients. Fluid balance charts were maintained in all patients. Most of the patients (58.6%) were euvolaemic, 33.2% were hypovolaemia and 8.6% were hypervolaemic.

SIADH was found in 6% (13) patients. Four were labelled as having SIADH by the treating physicians. The other 9 had laboratory evidence of SIADH and fulfilled the diagnostic criteria for this condition. There were another 7 who had biochemical profile suggestive of SIADH but did not have either thyroid function tests or cortisol levels to fulfill the criteria entirely.

DISCUSSION

In this study, a quarter of patients presented with neurological symptoms though their initial sodium concentrations were not different from the rest of the group. In such a retrospective study, it is difficult to ascertain whether the neurological symptoms were due to the underlying illness or by hyponatraemia alone or by a combination of both. The severity of symptoms and signs of hyponatraemia depend not only on the degree of sodium depletion but also on the rapidity of fall of plasma sodium. Patients with mild hyponatraemia (sodium upto 130 mmol/L) are almost always asymptomatic. Serum sodium levels between 125-130 mmol/L may be associated with anorexia, nausea, vomiting and abdominal cramps. Severe hyponatraemia, with serum sodium level less than 125 mmol/L may cause neurological symptoms including agitation, confusion and hallucinations. With levels of sodium less than 115 mmol/L, there is the risk of seizures and coma.[8]

Hyponatraemia of rapid onset is associated with cerebral oedema raised intracranial pressure and subsequent decrease in cerebral blood flow leads to cerebral symptoms.[9] In contrast, chronic hyponatraemia i.e > 48 hours duration allows slow adaptation to the low plasma osmolality and, therefore, prevention of cerebral oedema.[10] There remains a controversy whether stable severe hyponatraemia is associated with brain damage. In this study, patients who had expired had lower initial serum sodium levels and longer mean duration of stay in hospital.

It was observed that investigations were not done sequentially and serum osmolality was not matched with urine osmolality and spot urine sodium. Moreover, the latter two were checked in upto 50% patients only. The diagnosis of SIADH needs certain criteria to be fulfilled, which include hyponatraemia with hypo-osmolality and excessive renal sodium excretion in an euvolaemic patient with normal thyroid and adrenal function.[11] Cortisol and thyroid function tests were not done in 7 patients in whom there was a strong suspicion of SIADH while in this study, charts were well-maintained in all patients. Previous studies have reported fluid balance chart maintenance as low as 17% and 40% only.[12,13]

Hyponatraemia is known to occur more frequently in the elderly as seen in this study.[12-14] The aetiology of hyponatraemia was most definitely multifactorial with GI losses accompanied by use of diuretics and ACE I inhibitors topping the list. Ageing is associated with reduced cardiac and renal reserve and a reduced ability to compensate for fluctuations in environmental conditions. In many cases, this may be coupled with iatrogenic causes such as the use of diuretics or medicine which impair the intake of food and fluid. Use of diuretics being one of the major causes of hyponatraemia, has also been reported by Saeed[13] and Crook.[12]

Prior to treatment, the volume status of the patient needs to be assessed.[15] Broadly speaking for hypovolaemic patients, diuretics need to be stopped and the intravascular volume be restored with normal saline. For normovolaemic patients, hypothyroidism and glucocorticoid deficiency are to be excluded with restricted fluid intake. Demeclocycline should be considered for SIADH. For hypervolaemic patient, there is a need to treat the underlying condition whether it may be cardiac, hepatic or renal. These patients need salt and water restriction and diuretics may also be considered. Asymtomatic hyponatraemia may not require treatment with hypertonic saline, especially if sodium levels are greater than 120 mmol/L. Fluid restriction may be beneficial though the rate of increase in sodium level is slow at upto 1.5 mmol/L/24 hours.[4]

Patients with an underlying cause should be treated for the primary cause. On the contrary, patients with symptomatic hyponatraemia need hypertonic saline. Mortality and morbidity associated with treatment with fluid restriction has been high.[16]

Normal saline was administered to most of the patients,

however, those with chronic liver disease received 5% dextrose, which is isotonic and acts like pure water due to the rapid clearance of dextrose. It can be detrimental to patients with severe hyponatraemia. The prevalence of hyponatraemia in patients with decompensated cirrhosis may be upto 48%.[17,18] Patients with congestive heart failure and cirrhosis have diminished "effective" circulatory volume and, therefore, increased levels of ADH.[19] Treatment of hyponatraemia in these patients is, therefore, difficult and not always adequate. The mainstay of treatment in such patients being fluid restriction and use of diuretics by improvement in the intravascular reserve. In SIADH, the first line treatment is fluid restriction. Isotonic saline has a limited role in SIADH as the urine osmolality is >300 mOsmol/kg H_2O and the osmolality of fluid administered should be greater than the urine osmolality.[19] Demeclocycline is the treatment of choice for treatment of SIADH and acts by causing nephrogenic Diabetes insipidus.[20] Other more uncommon causes of hyponatraemia such as cerebral salt wasting and sick cell syndrome should be considered and is associated with a demonstrable plasma osmolar gap.

In this study, 7.7% patients had sodium corrected at a rate of >15 mmol/L/24 hours and at a rate of 10 to 15 mmol/L/24 hours in another 9.5%. This, however, may prove to be detrimental to the patient and correction be done at a properly adjusted rate.

There has also been controversy regarding the rate of correction of hyponatraemia due to the risk of development of CPM (central pontine myelinosis) if rapid correction of hyponatraemia is undertaken. Arieff advocates rapid correction within certain defined parameters. Sterns recommends a more conservative approach.[5,10] However, a moderate approach should be adopted as suggested by Ellis[21] at a rate of correction of less than 10 mmol/L in 24 hours.[16] Hojer[22] suggested that chronic hyponatraemia be corrected slowly at a rate of 0.5 mmol/L/hour as the brain has adapted to the hypotonic extracellular environment and rapid correction in this case will lead to demyelination.[17] In acute hyponatraemia, there is a high risk of cerebral oedema, therefore, rapid correction with hypertonic saline preferably with a loop diuretic at a rate of 1-2 mmol/L/hour should be undertaken.[4,8,22,23] Inadequate treatment of symptomatic hyponatraemia may result in significant morbidity.[24] There is a lack of randomized controlled trial in this arena and this study had the limitation of being a retrospective analysis with incomplete documentation. Further studies need to be carried out on a prospective basis, which may in turn help to improve the clinical practice.

CONCLUSION

Hyponatraemia is a common electrolyte disturbance. It can be well-diagnosed with a history of concurrent illness and medications accompanied by an assessment of extracellular volume on physical examination. This needs to be accompanied by relevant biochemical profile as the treatment given depends on the aetiology. If hyponatraemia is inadequately investigated, the management instituted may actually be inappropriate and inadequate. Management includes immediate treatment in patients with acute severe hyponatraemia because of risk of cerebral oedema and hyponatraemic encephalopathy. Chronic hyponatraemia requires fluid restriction and rapid correction needs to be avoided to reduce the risk of central pontine myelinosis.

REFERENCES

1. Chung HM, Kluge R, Schrier RW, Anderson RJ. Postoperative hyponatremia: a prospective study. *Arch Intern Med* 1986; **146**: 333-6.
2. Ayus JC, Wheeler JM, Arieff AI. Postoperative hyponatremic encephalopathy in menstruant women. *Ann Intern Med* 1992; **117**: 891-7.
3. Arieff AI. Management of hyponatraemia. *BMJ* 1993; **307**:305-8.
4. Gill GV, Clear CTG. Hyponatraemia. In: Price CP, Alberti KGMM, (edi). Recent advances in clinical biochemistry. London: *Churchill Livingstone*; 1985.p.149-77.
5. Baran D, Hutchinson TA. The outcome of hyponatremia in a general hospital population. *Clin Nephrol* 1984; **22**:72-6.
6. Arieff AI. Hyponatremia, convulsions, respiratory arrest and permanent brain damage after elective surgery in healthy women. *N Engl J Med* 1986; **314**:1529-35.
7. Kennedy PG, Mitchell DM, Hoffbrand BI. Severe hyponatraemia in hospital in patients. *Br Med J* 1978; **2**: 1251-3.
8. Smith DM, McKenna K, Thompson CJ. Hyponatraemia. *Clin Endocrinol (Oxf)* 2000; **52**: 667-78.
9. Illowsky BP, Laureno R. Encephalopathy and myelinolysis after rapid correction of hyponatraemia. *Brain* 1987; **110** (pt4):855-67.
10. Sterns RH. The treatment of hyponatremia: first, do no harm. *Am J Med* 1990; **88**: 557-60.
11. Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of antidiuretic hormone. *Am J Med* 1967; **42**:790-806.
12. Crook MA, Velauthar U, Moran L, Griffiths W. Review of investigation and management of severe hyponatraemia in a hospital population. *Ann Clin Biochem* 1999; **36** (pt2):158-62.
13. Saeed BO, Beaumont D, Handley GH, Weaver JU. Severe hyponatraemia: investigation and management in a district general hospital. *J Clin Pathol* 2002; **55**: 893-96.
14. Tolias CM. Severe hyponatraemia in elderly patients: cause for concern. *Ann R Coll Surg Engl* 1996; **77**: 346-8.
15. Reynolds RM, Seckl JR. Hyponatraemia for the clinical endocrinologist. *Clin Endocrinol (Oxf)* 2005; **63**: 366-74.
16. Ayus JC, Krothapalli RK, Arieff AI. Treatment of symptomatic hyponatremia and its relation to brain damage: a prospective study. *N Engl J Med* 1987; **317**:1190-5.
17. Papadakis MA, Arieff AI. Hyponatraemia and hypernatraemia in liver disease. In: Epstein M, (edi). The kidney in liver disease. 3rd ed. Baltimore: *Williams & Wilkins*; 1988.p.73-88.

18. Wilkinson SP, Blendis LM, Williams R. Frequency and type of renal and electrolyte disorders in fulminant hepatic failure. *Br Med J* 1974; **1**:186-9.

19. Janicic N, Verbalis JG. Evaluation and management of hypo-osmolality in hospitalized patients. *Endocrinol Metab Clin North Am* 2003; **32**: 459-81.

20. Forrest JN Jr, Cox M, Hong C, Morrison G, Bia M, Singer I. Superiority of demeclocycline over lithium in the treatment of chronic syndrome of inappropriate secretion of antidiuretic hormone. *N Engl J Med* 1978; **298**:173-7.

21. Ellis SJ. Severe hyponatraemia: complications and treatment. *QJM* 1995; **88**:905-9.

22. Hojer J. Management of symptomatic hyponatraemia: dependence on the duration of development. *J Intern Med* 1994; **235**:497-501.

23. Gill G, Leese G. Hyponatraemia: biochemical and clinical perspectives. *Postgrad Med J* 1998; **74**:516-23.

24. Arieff Al, Ayus JC, Fraser CL. Hyponatraemia and death or permanent brain damage in healthy children. *BMJ* 1992; **304**:1218-22.