Clinical Algorithms

Hyponatraemia

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A common finding on biochemical screening, hyponatraemia may be a symptom of underlying systemic illness but seldom requires specific treatment and only rarely demands urgent correction. The laboratory at this hospital sees low serum sodium concentrations in about a quarter of all multichannel biochemical analyses. For example, in 1983, of 73 950 analyses carried out in 21 137 patients, 15 075 (20.4%) showed sodium concentrations of 130-137 mmol(mEq)/l, 1973 (2.7%) concentrations of 120-129 mmol/l, 157 (0.2%) concentrations of 110-119, and 26 (0.04%) concentrations of less than 110 mmol/l. As patients with hyponatraemia are likely to undergo repeated analyses these figures tend to overestimate the incidence of serious hyponatraemia but, nevertheless, illustrate its relative rarity.

Causes

In many cases hyponatraemia is the appropriate and obligatory end point following a variety of challenges to healthy homeostatic mechanisms that maintain, primarily, circulating volume, intracellular and extracellular osmolality and electrochemical balance. Mechanisms underlying hyponatraemia have been more fully described by Flear *et al*¹ and Goldberg.² The table shows, and expands, a simple classification, adapted from Berl *et al*.³ That causes and causative mechanisms often coexist should be borne in mind.

PSEUDOHYPONATRAEMIA

Proteins and lipids normally occupy a small fraction of total plasma volume. Sodium is distributed within the remaining plasma water fraction. Gross hyperlipidaemia or paraproteinaemia, by "diluting" plasma water, may result in apparent hyponatraemia (a fall of 30 mmol/l or more may be seen) when analysis is carried out by flame spectrophotometry (as is usually the case). Hyponatraemia in this case is clearly artificial and does not reflect serum hypotonicity. Ultracentrifugation of the sample, or (if available) use of an ion selective electrode, will give a sodium concentration corresponding to its osmotic activity in plasma.

NON-HYPOTONIC HYPONATRAEMIA

In these conditions hyponatraemia is the result of either:

(1) The presence in plasma of an osmotically active substance that penetrates cells poorly, thereby setting up a concentration gradient along which redistribution of intracellular water occurs. Such substances include glucose and mannitol. Although urea and alcohol are occasionally considered to be in this category, both penetrate cells rapidly, and prolonged excess of either is therefore unlikely to cause appreciable hyponatraemia.

(2) The presence in plasma of non-diffusible and ordinarily intracellular anions as a result of leakage through dysfunctioning cell membranes—the "sick cell syndrome." In various severe illnesses, including congestive cardiac failure, liver failure, burns, and septicaemia, hyponatraemia can occur acutely, without weight gain, and in the presence of normal serum osmolality. Flear and Singh⁴ have suggested that sick cells not only fail metabolically to produce sufficient non-diffusible intracellular anions to maintain intracellular osmolality (thereby giving rise to hypotonic hyponatraemia in the long term) but also leak such osmotically active anions into plasma. Water follows and, in restoring plasma osmolality, gives rise to hyponatraemia. (Osmolality is usually measured in the laboratory by assessing freezing point depression. The usual method of estimating serum osmolality ($2 \times (\text{sodium} + \text{potassium}) + \text{glucose} + \text{urea}$ with all values in mmol/l) does not take into account these unmeasured anions and therefore may underestimate serum osmolality, giving rise to an "osmolal gap"—that is, measured osmolality minus estimated osmolality.)

The existence of the sick cell syndrome has been questioned, and, indeed, the diagnosis can be difficult to establish. Solute leaks and consequent water shifts are often transient phenomena, influenced by solute diuresis and taking place against a background of other mechanisms of hyponatraemia (including inappropriate antidiuresis, diuretic treatment, hypovolaemia, paracentesis, and others). The osmolal gap, itself difficult to estimate accurately, can therefore vary widely from day to day. Nevertheless, the concept of the sick cell syndrome has gained general acceptance. Its existence in the context of rapidly developing hyponatraemia without weight gain (even in the face of detectable antidiuretic hormone concentrations) with normal serum osmolality and a positive osmolal gap is supported by the success (albeit variable) of membrane restorative glucose, insulin, and potassium treatment in the illnesses referred to above.

It is important to appreciate that in both (1) and (2) above hyponatraemia exists in the presence of normal serum osmolality. Measures directed at restoring normonatraemia alone are therefore inappropriate.

HYPOTONIC HYPONATRAEMIA

Inappropriate antidiuretic hormone secretion—This term should be restricted to disorders in which truly autonomous hypersecretion of antidiuretic hormone occurs. This is usually found in relation to neoplastic or granulomatous disorders, small cell lung cancer being

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the commonest single cause. The term is also used, loosely, when antidiuretic hormone concentrations are raised (or detectable) in the face of reduced plasma osmolality. In such cases, however, release of antidiuretic hormone is the appropriate response to a non-osmolal stimulus (for example, hypovolaemia). The box shows some causes of inappropriate antidiuresis. In acute asthma, intermittent positive pressure ventilation, and Guillain-Barré syndrome antidiuretic hormone may be released in response to diminished systemic venous return (in the same way that hypovolaemia stimulates antidiuretic hormone release). These are therefore probably not examples of the syndrome of inappropriate

antidiuretic hormone secretion but are included here for completeness. The syndrome is usually defined by the following criteria: (1) hypotonic hyponatraemia, (2) inappropriately high urine osmolality, and (3) continued natriuresis (for example, >20 mmol/l, given continued salt intake), (4) in the absence of hypovolaemia, cardiac, renal, adrenal, or pituitary disease, or diuretic treatment, and (5) clinical and biochemical improvement after fluid restriction. The diagnosis is most simply and safely confirmed by measuring serum antidiuretic hormone concentrations when this assay is available. It should not be necessary to resort to potentially hazardous water challenge.

Classification and causes of hyponatraemia

Type	Cause	Typical urinary sodium concentration (mmol/l)
Spurious Pseudohyponatraemia (dilutional hyponatraemia)	Downstream from intravenous infusion Hyperlipidaemia Paraproteinaemia	
True Non-hypotonic	Hyperglycaemia Alcohol Mannitol "Sick cell syndrome"	
Hypotonic Extracellular fluid depletion*		
Renal	Diuretics Mineralocorticoid deficiency (Addison's) Salt losing nephropathies Proximal renal tubular acidosis	>20
Extrarenal (external loss or internal sequestration)	Vomiting, diarrhoea Burns, muscle trauma Pancreatitis, peritonitis, ileus	<10
Normal/near normal extracellular fluid volume		
Acute	Water intoxication (including administration of hypotonic solutions) particularly in the presence of pain, hypovolaemia, recent surgery, labour, schizophrenia	
Chronic	Syndrome of inappropriate antidiuretic hormone secretion Glucocorticoid deficiency Hypothyroidism Chronic renal disease "Reset osmostat"/age	>20
Oedematous states (extracellular fluid volume increased)†	Nephrotic syndrome Congestive cardiac failure Cirrhosis	<10 (>20 in renal failure)
Drug induced	Malnutrition/malabsorption/enteropathic protein loss	
Sodium depletion		
Stimulation of antidiuretic hormone release	Diuretics Carbamazepine Narcotics Chlorpromazine Chlorpropamide Vincristine, vinblastine Desmopressin, oxytocin Chlorpropamide, tolbutamide, biguanides Cyclophosphamide Colchicine	
Intrinsic antidiuretic hormone activity		
Enhanced antidiuretic hormone activity		
Uncertain action		

Conversion: SI to traditional units—Sodium: 1 mmol/l = 1 mEq/l.

*Whole body sodium content decreased, whole body water content mildly decreased.

†Whole body sodium content mildly increased, whole body water content greatly increased.

Causes of inappropriate secretion of antidiuretic hormone

Tumours	Bronchus Prostate Thymus Pancreas Brain
Central nervous disorders	Head injury Neurosurgery Cerebrovascular accidents Meningitis Cerebral lupus
Chest disorders	Severe pneumonias Pulmonary tuberculosis Fungal infections Acute asthma Intermittent positive pressure ventilation
Others	Hypothyroidism Guillain-Barré syndrome Disseminated varicella zoster Maxillofacial injury/surgery Acute intermittent porphyria Alcohol withdrawal Reset osmostat/increasing age

Effects

The symptoms and signs of hyponatraemia are generally non-specific. Central nervous system effects are most important; these range from disorientation to major disturbances of brain stem and higher cerebral function, seizures, and, potentially, death. Although such effects are unusual at sodium concentrations greater than 120 mmol/l; there is no consistent relation between clinical features and degree of hyponatraemia. The speed of onset of hyponatraemia, on the other hand, matches closely the severity of effects. Chronic hyponatraemia of, for example, 115 mmol/l may be silent, but the effects of a fall to this concentration from normal over a few hours may well be life threatening.

Treatment

The algorithm outlines treatment. Proper assessment and management of the underlying problem is clearly central, and, except in emergency cases, initial investigation and treatment should be aimed at the root cause. Hyponatraemia itself seldom requires treatment. In general, extracellular fluid volume depletion requires isotonic fluid replacement, while extracellular fluid volume expansion (both modest and severe) requires water restriction.

Hyponatraemia 1

Hyponatraemia 2

Severe hyponatraemia is a medical emergency with high mortality and morbidity. Residual central nervous system deficit is its major long term hazard. As water intoxication is the usual root cause and as rapidly progressing hyponatraemia induces the most severe clinical features the logical approach would appear to be to restrict fluid intake and aim for a gradual return to normonatraemia. When symptoms and signs are mild such a conservative approach is sensible. The safest and most effective course of action when major central nervous system manifestations are present is still, however, open to debate. Hypertonic saline is the most effective treatment but may be hazardous, for example, in the presence of impaired cardiac reserve.

Whether residual central nervous system injury (including the uncommon and controversial finding of central pontine myelinolysis) is more likely when normonatraemia is rapidly restored or whether prolonged exposure to severe hyponatraemia is more damaging to neural tissue cannot confidently be answered at present. Recent experience suggests that rapid restoration of serum sodium concentration (at around 2.5 mmol/l/h) is preferable to slow restoration over 24 hours or more. Two alternative schemes for hypertonic saline infusion are given in the algorithm; the choice is still somewhat empirical.

When small cell carcinoma is the underlying cause inappropriate antidiuretic hormone secretion generally responds to combination chemotherapy, which should therefore be started early. Fluid restriction and, occasionally, demeclocycline may be necessary in acute cases but can usually be stopped after a few weeks.

When, in other conditions, persistently inappropriate antidiuresis causes symptomatic hyponatraemia despite fluid restriction drug treatment may be needed. Of the available agents, demeclocycline is currently the treatment of choice. The converting enzyme inhibitor captopril has been used successfully in the management of severe hyponatraemia associated with congestive cardiac failure. The use of glucose, insulin, or potassium treatment in acute cases of this and other causes of the sick cell syndrome has already been mentioned.

Points to note

(1) Hyponatraemia is common. Serious hyponatraemia is not. Investigation is often not warranted and specific treatment often unnecessary and occasionally hazardous.

(2) Hyponatraemia does not necessarily imply either hypo-osmolality or sodium depletion.

(3) Hyponatraemia is often the appropriate response by healthy homeostatic mechanisms to a variety of osmotic and non-osmotic stimuli.

(4) Rapid transcellular fluid shifts are probably more hazardous than chronic stable hyponatraemia. Bear this in mind in planning treatment.

(5) A firm diagnosis may not be possible, but a working diagnosis will be reached by asking these questions: Is emergency treatment necessary? If not, is this true hyponatraemia? Is this hypotonic hyponatraemia? If hypotonic, is the patient volume depleted or oedematous?

(6) Causes coexist; the diagnosis may therefore be incomplete and (as diseases seldom behave entirely as they should and as interpretation can be difficult even when they do) may even be incorrect. Keep an open mind. The following are easily missed: inappropriate antidiuretic hormone secretion; adrenal insufficiency (careful, this may mimic inappropriate antidiuretic hormone secretion); the sick cell syndrome; occult non-renal sodium depletion (especially in those who are elderly or malnourished, or both); and drug effects.

I thank Miss Anne Macleod for the local biochemical data.

References

- 1 Fleck CTG, Gill GV, Burn J. Hyponatraemia: mechanisms and management. *Lancet* 1981;iii:26-31.
- 2 Goldberg M. Hyponatraemia. *Med Clin North Am* 1981;65:251-69.
- 3 Berl T, Anderson RJ, McDonald KM, Schrier RW. Clinical disorders of water metabolism. *Kidney Int* 1976;10:117-32.
- 4 Fleck CTG, Singh CM. Hyponatraemia and sick cells. *Br J Anaesth* 1973;45:976-94.

MATERIA NON MEDICA

Prophecies, witches, and knells

It was recently announced that Knaresborough Zoo may be permanently closed, and this reminded me that Mother Shipton of prophecy fame came from Knaresborough, and for nearly 20 years I have regularly passed the Dropping Well and the cave which is her legendary home.

Her prophecies are written in a book published in 1686, nearly two hundred years after her birth in 1488, and there are further manuscripts in the possession of the Duke of Northumberland, dated 1613, which refer to her. Some of her prophecies have a strangely modern ring: "Carriages without horses shall go/And accidents fill the world with woe" (motor vehicles and road accidents?); "Around the world thoughts shall fly/In the twinkling of an eye" (communication satellite?); "Under water men shall walk,/Shall ride, shall sleep, shall talk" (skin divers, submarines?); "In the air men shall be seen/In white, in black, and in green" (aeroplanes, parachutists?); "Taxes for blood and for War/Will come to every door" (Income tax? it was first levied in 1806 to help pay for war).

The Shipton prophecies range from foretelling the era of railway trains to the fate of the kings and queens of England for several hundred years after her own death. Samuel Pepys, describing in his diary the great fire at the beginning of September 1666, wrote, "Sec, Mother Shipton's word is out," meaning that she had prophesied the disaster. A second prophecy, "Triumphant Death rides London through," occurs four lines after the reference to the restoration of the monarchy in 1660 and describes the great plague of 1665. When a patient believes he can foretell the future some psychiatrists label him as having the "Mother Shipton syndrome."

Threatened that she would be burnt as a witch, Mother Shipton threw her well washed head scarf on the fire, saying, "If this burn so shall I." Although

it lay in the fire for several minutes it was not even singed. The explanation is that the water supply to the cave is an almost saturated solution of calcium sulphate which deposits a film of lime over everything with which it comes in contact. As a result of regular washing in the water, the head covering would have become gradually petrified, and therefore fireproof.

Next to the cave is an outcrop of magnesium limestone over which the water flows to a pool near the well. Water with a high content of calcium sulphate passing over magnesium limestone will probably end up with a reasonable amount of magnesium sulphate (Epsom Salts) in it—an excellent saline purgative. This may or may not be the case, but "keeping regular" is one of many reasons given for longevity. Mother Shipton, who died in 1561 at the then ripe old age of 73, presumably drank copiously of the water. She was buried on the outskirts of York in unconsecrated ground, as was the normal practice in the Middle Ages for "witches." Unfortunately, no trace of her burial place can now be found.—JAMES DUNLOP, district medical officer, Hull.

Correction

Pocket computers: a new aid to nutritional support

We regret that two errors occurred in this paper by Dr C M Colley *et al* (11 May, p 1403). Firstly, the legends to figures 2 and 3 should be transposed. Secondly, in the fifth paragraph of the Discussion the first sentence should have read "... and in these the measured resting energy expenditure provided a good estimate of their total energy requirement."