Evaluation of hyponatraemia: is there a rational approach?

P. Gross¹ and J. Hensen²

Departments of Medicine, ¹Universitätsklinikum C. G. Carus, Dresden and ²Friedrich-Alexander Universität, Erlangen-Nürnberg, FRG

The last 5 years have seen a stream of publications—in excess of 100 per year—dealing with hyponatraemia. These reports were remarkable for two reasons: (i) they indicated unresolved clinical problems in the handling of severe symptomatic hyponatraemia, and (ii) for the first time they announced orally available non-peptide vasopressin antagonists. To put these developments into perspective we would first like to outline the accepted approach to hyponatraemia.

Hyponatraemia—water excess and not (necessarily) sodium deficit

Hyponatraemia in general is well established to be a consequence of a disturbance in water balance. Physiological normonatraemia is maintained by an integrated system involving precise regulation of water intake via thirst and control of water excretion via vasopressin. Hyponatraemia is almost always secondary to defects in water excretion mediated by vasopressin. Therefore the rational approach to hyponatraemia revolves around the question: what is the cause of the abnormal vasopressin (ADH) stimulation?

Abnormal (non-osmotic) vasopressin secretion is observed in two different circumstances: (i) dysregulation of cells producing vasopressin; (ii) arterial baroreceptor mediation of vasopressin. The first type of abnormality is the cause of hyponatraemia in the classical syndrome of inappropriate antidiuretic hormone (SIADH), while baroreceptor-mediated vasopressin secretion is typically found in the hyponatraemia of liver cirrhosis, cardiac failure, and plasma volume deficiency. The two entities are easy to distinguish in clinical practice. SIADH is characterized by signs of mild plasma volume expansion, while the opposite applies to the settings of baroreceptor-mediated vasopressin secretion.

The patient with SIADH

Patients with SIADH will consequently have a normal blood pressure and they will barely be oedematous. They are remarkable for their high normal glomerular filtration rate reflected in strikingly low concentrations of creatinine, urea, urate, and phosphate in plasma. In the same vein they will excrete average to high amounts of sodium in the urine, often in excess of 100 mM/24 h, and they are usually not receiving diuretics. The urinary concentration will be less than maximally dilute; most patients will actually produce a concentrated urine with osmolalities ranging between 300 and 600 mOsm/kg.

On the basis of animal experiments, all of the changes typical of SIADH have been explained by the primary overproduction of vasopressin when it was combined with an average fluid intake. Indeed it was a surprising finding in SIADH that such patients spontaneously maintained an average or an elevated fluid intake despite their hyponatraemic hypo-osmolality, indicating an associated disturbance of thirst. When measured, the plasma vasopressin concentration in SIADH was similarly abnormal, i.e. it was not suppressed despite the presence of hypo-osmolality (hyponatraemia). This turned out to be a general feature of hyponatremia; plasma vasopressin will thus be worthless in the distinction between different causes of hyponatraemia.

Patients with SIADH tend to develop the lowest plasma sodium concentrations observed and even readings below 110 or 100 mM/l are not unheard of. SIADH occurs in typical clinical settings. There is usually a central nervous system disorder (encephalitis, meningitis, brain tumour, cerebrovascular accident, subarachnoid haemorrhage), a neoplasm (bronchogenic carcinoma, pancreatic carcinoma, or other malignancy) or a pulmonary disturbance (pneumonia, abscess, tuberculosis, aspergillosis, etc.) Vasopressin overproduction comes about either by paraneoplastic vasopressin secretion from tumour cells or by excessive hypothalamic vasopressin secretion secondary to stimulation or irritation of neurons (e.g. in the brain or in the lung) physiologically feeding information into the hypothalamus.

The patient with compromised arterial filling

A different mechanism of abnormal (non-osmotic) vasopressin secretion is responsible for the hyponatraemia that often accompanies advanced stages of liver cirrhosis, cardiac failure, and intravascular volume deficiency. This mechanism is now attributable to baroreceptor involvement. In normal physiology in healthy human subjects baroreceptor activity was shown to be without effect on vasopressin. However, after extreme changes, such as after induction of hypo-
tension baroreceptor-mediated vasopressin stimulation was definitely observed even in normal individuals. It was therefore interesting to utilize tests of baroreceptor function (lower body negative pressure, thermonutral water immersion, tilt table orthostasis, neck chamber suction) in the analysis of disease states such as hyponatraemic—compared with normonatraemic—liver cirrhosis, cardiac failure and intravascular volume deficiency. Collectively these studies showed vasopressin to be prominently stimulated by baroreceptor mechanisms solely in the hyponatraemic but not in the normonatraemic varieties of these disorders [1].

In contrast the adrenergic nervous system and the renin–angiotensin system were under baroreceptor control in hyponatraemia and normonatraemia alike. Furthermore hyponatraemic patients had lower mean arterial pressures and were in more advanced stages of their underlying diseases (cirrhosis, cardiac failure) than their normonatraemic counterparts. Therefore the studies suggested that vasopressin stimulation was a consequence of severe circulatory compromise, serious enough to be signalled by baroreceptors. Hyponatraemia basically resulted as hydro-osmotic ‘side effect’ of this vasopressin when patients with advanced cirrhosis, cardiac failure and volume deficiency satisfied their characteristically increased thirst by avid drinking.

Clinically this type of hyponatraemia is the nephrologist’s daily routine; in fact it has turned out to be the commonest electrolyte disorder in clinical practice. Based on the features described above this hyponatraemia is clearly distinguished from SIADH. Thus, the patient’s circulatory compromise will be obvious. The blood pressure will be inadequately low for the patient’s age. (If measurements of catecholamines, renin (PRA) or aldosterone are obtained, the readings will show highly abnormal stimulation.) The reduced glomerular filtration rate will result in plasma concentrations of creatinine, urea, urate, and phosphate that are increased while the spontaneous sodium excretion rate will be low (<20 mmol/l). Finally the patients will have a medical history of liver cirrhosis, cardiac failure, or fluid loss (diarrhoea, vomiting, excessive use of diuretics) that will be difficult to miss.

The patient with renal failure and with pseudohyponatraemia

Occasionally, none of the syndromes described above appear to apply to a given hyponatraemia. In such cases advanced renal insufficiency (plasma creatinine >500 μM/l) in a patient with a high fluid intake should be considered first. The kidney’s ability to excrete water is limited to a maximum of 20% of the glomerular filtration rate—even in the absence of ADH. A patient with a GFR of 5 ml/min will be unable to excrete more than 1.4 l/24 h of water. If this patient consumed 2.5 l/24 h approximately 1 l of water would remain in his body, diluting the serum sodium concentration and eventually causing hyponatraemia if this volume of a fluid intake were maintained.

Next, profound hyperglycaemia is sometimes encountered as a cause of hyponatraemia. The latter is related to water shifting out of glucose impermeant cells into the hyperglycemic extracellular fluid. Rarely, profound hyperlipidaemia or hyperproteinaemia are responsible for a measured hyponatraemia. This phenomenon is an error of autoanalysers. Their setup commonly assumes that no more than a fixed small volume of plasma is being occupied by proteins and lipids while the remaining plasma volume is assumed to be the sodium space. Accordingly the error will be uncovered by a measurement of plasma osmolality which ought to be normal. Finally, hypothyroidism, glucocorticoid deficiency, hypopituitarism, psychosis, and some psychoactive drugs have also been described as rare settings of hyponatraemia.

Does ANP cause the hyponatraemia in cerebral salt wasting?

In the pathogenesis of hyponatraemia one group of hormones still in search of a role are the natriuretic hormones. It had been suggested that they might cause hyponatraemia in the setting of cerebral pathology, in which ‘cerebral salt wasting’ is sometimes observed. This was suspected of inducing hyponatraemia. However, no convincing evidence has been forthcoming. In each instance of hyponatraemic ‘cerebral salt wasting’ where such data was sought antidiuretic hormone (ADH) was detectable rather than suppressed [2]. Based on available evidence ADH therefore continues to provide a sufficient explanation for the hyponatraemia associated with ‘cerebral salt wasting’.

Vasopressin is the culprit—do rational therapeutic strategies emerge

Taking all aspects together it is apparent that the plasma vasopressin concentration is the culprit of most cases of hyponatraemia. This becomes a relevant aspect in the treatment of severe, symptomatic hyponatraemia, especially when the presence of confusion or coma demand action. Until recently established practice was to impose a fluid restriction, to improve the underlying condition, to make a cautious attempt of treating baroreceptor hyponatraemia with hypertonic saline, whereas frusemide plus i.v. replacement of urinary sodium losses (using hypertonic saline) were recommended in SIADH. However, these treatments may take too much time to work, or they may be unsatisfactory altogether. Therefore an alternative approach, perhaps using vasopressin antagonists, had long been awaited. It was in fact possible to synthesize vasopressin analogues with antagonistic properties. However, the initial agents were unsuitable for clinical application. Those antagonists had to be given parenterally. Furthermore their effects—although well established...
in laboratory animals—were unpredictable in humans. The situation is now changing. A new class of hydro-osmotic vasopressin antagonists has just been described [3,4]. The agents are orally available because of their non-peptide structure. Trials in patients with hyponatraemia are in progress in Japan and have recently been reported in preliminary form (personally communicated by T. Saito, Tochigi). It is fair to expect improvements in the treatment of acute and chronic hyponatraemia when these and other antagonists will become more generally available.

How rapidly should hyponatraemia be corrected?

If new vasopressin antagonists gave us an effective tool to manipulate the serum sodium concentration, how rapidly are we going to proceed when correcting a hyponatraemia? A few years ago severely hyponatraemic patients were sometimes observed to be affected by cerebral—pontine or extrapontine—myelinolysis of unknown cause. It was feared that the persistence of hyponatraemia or the rapid correction of the latter caused the myelinolysis. Subsequent work has largely clarified the issues. Several studies of patients documented that severe hyponatraemia (< 110 mM/l) per se was the major risk factor for brain damage [5]—while a rapid increase of the serum sodium concentration from severely hyponatraemic to mildly hyponatraemic levels was safe. Severe hyponatraemia is associated with brain swelling, metabolic changes of brain cells, and cerebral hypoxia. These phenomena are of particular relevance to the hyponatraemia of young menstruant women. Taken together therapy of severe symptomatic hyponatraemia should never be delayed; instead it should be approached with high priority. An hourly rate of correction of 1–2 mM/l appears appropriate. A final serum sodium concentration of approximately 130 mM/l should initially suffice, and care should be taken to avoid overcorrection to hypernatraemic levels. Treatment of hyponatraemia has been performed along these guidelines in at least 62 documented cases and no brain damage was observed [5].

In summary it is the role of vasopressin that permits a rational approach to the cause of a given hyponatraemia. In addition it now also provides a rationale for treatments with future vasopressin antagonists.

Note added in proof:


References


Blood volume preservation in dialysis: tools and strategies

H. A. Koomans and P. J. Blankestijn

Department of Nephrology and Hypertension, University Hospital Utrecht, The Netherlands

Although strategies for its prevention improve, haemodialysis hypotension continues to be a major concern of the nephrologist. A multifactorial genesis is generally assumed, but the key factor must be circulatory underfilling. Underfilling results from progressive haemoconcentration by sustained ultrafiltration and intracellular water shift, superimposed on the burden of the obligatory extracorporeal circuit. Ultrafiltration is of course an unavoidable therapeutic measure taken to establish physiological correction of the interdialytic gain in volume, and subsequently in blood pressure. Some patients, however, respond with sudden hypotension, which is definitely non-physiological and felt as torment rather than therapy.

Why does sudden hypotension occur? Progressive haemoconcentration automatically leads to decreased venous return and cardiac output. Initially, as in haemorrhage, blood pressure is maintained by sympathetic activation causing tachycardia and vasoconstriction. Sudden hypotension occurs when intravascular volume and venous return have reached...