Water balance and hyponatraemia

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Water balance and its control in man in health and disease has been the subject of many studies and reviews (Berl, Anderson, McDonald & Schrier, 1976; Robertson, 1977). However, disorders of water balance, in particular hyponatraemia, continue to cause difficulty in clinical practice.

Our aim is to consider the physiological purpose of water balance, and what makes the patient ill when water balance is abnormal, and on that basis to attempt to define the relationship between hyponatraemia and the clinical effects of water overload. Water depletion and thirst are not discussed here.

Physiological background

Verney (1948) showed that hyperosmolar solutions of sodium chloride and other substances injected into the carotid artery caused a decrease in urine flow and indirect evidence suggested this was due to an increased secretion of antidiuretic hormone from the pituitary gland. He suggested that there were specialized cells (osmoreceptors) within the distribution zone of the internal carotid artery, which responded to a change in the osmolality of the extracellular fluid and caused a change in the secretion of antidiuretic hormone. Robertson, Klein, Roth & Gordon (1970) developed an assay which allowed them to examine the effect of hyperosmolar solutions on the plasma concentration of the human antidiuretic hormone, arginine vasopressin (AVP). These studies taken together demonstrate that when the plasma osmolality is increased with saline, sucrose or mannitol, there is an increase in plasma AVP. However, when the plasma osmolality is increased with urea or glucose, which can enter cells, there is no increase in plasma AVP. These findings demonstrate that it is not an increased plasma osmolality which stimulates AVP secretion, but that a gradient of osmolality between cells and extracellular fluid is probably at least a step in the stimulus to changing AVP secretion. In these acute experiments this gradient of osmolality will be temporary as water will move rapidly from the cells to re-establish equilibrium. It is therefore likely that it is the resulting reduction in cell volume, which, in some unknown way, leads to the increased secretion of AVP (Verney, 1948; Leaf, 1962). We have put cell volume as the controlled variable at the centre of a feedback system, which is therefore not osmoregulatory although it will respond to an acute change in the osmolality of the extracellular fluid.

The relations between these changes in plasma osmolality and urine water flow are determined by the components of the system, that is the relation between plasma osmolality and AVP secretion (the osmoreceptor response) and the relation between AVP and urine osmolality (the renal response). The osmoreceptor response can be defined in terms of the plasma osmolality at which plasma AVP increased (‘threshold’ or setting) and the subsequent change in plasma AVP for a given change in plasma osmolality (‘the responsiveness’) (Robertson, Mahr, Athar & Sinha, 1973; but see Moses, 1978). These responses are such that the urine flow can be halved or doubled if the plasma osmolality is changed by only 1% (2 mosmol/kg), which is a change in plasma sodium of only 1 mmol/l (Verney, 1948; Robertson, Shelton & Athar, 1976). The fall in plasma sodium which causes symptoms (10–15 mmol/l) is almost always
due to a defect within the system, as a very large intake of water (20 litres/day) would be required to produce it if the system was normal. When symptoms do occur they are neurological and are probably due to water-loading of cells, particularly the brain (Arieff, Llach & Massry, 1976). The renal system is inadequate to deal with water depletion because of the inevitable loss of water through the skin and lungs and it is for this reason that increased water intake through thirst is an essential response to increased osmolality of the body fluids.

The experiments of Verney and Robertson and his colleagues were acute ones concerned with transient uncompensated responses of the system, whereas many clinical problems are chronic states due to long-standing defects in the system. In health the osmolality of body fluids and the cell volume are kept almost constant at some chosen value (steady state), which requires that water excretion equals water intake. This is achieved by setting the urine osmolality to what is required for balance. Patients with a chronic hyponatraemia may contain relatively too much water, but the situation is not deteriorating otherwise the patient would not have survived. The patients are therefore in a steady or near-steady state, albeit an abnormal one (Levinsky, Davidson & Berliner, 1958; Leaf, 1962; Flear, 1970). In addition they may have few or no symptoms in spite of chronic hyponatraemia and hypo-osmolality (Wynn & Rob, 1954; Arieff et al., 1976).

A comparison of chronic hyponatraemia with acute hyponatraemia therefore suggests that two changes have taken place. If the initial water retention and hyponatraemia was due to an excessive AVP secretion and increased urine osmolality, then if the AVP secretion continued, a steady state could only be achieved if the excretion of water increased. Theoretically this could be achieved by an increase in the increase and excretion of osmotically active molecules, or by a fall in the renal responsiveness to AVP so that the urine osmolality falls to what is required for balance. A reduced renal responsiveness to AVP is common among patients with gross hyponatraemia (Leaf, 1962; Thomas, Morgan, Swaminathan, Ball & Lee, 1978).

The other change in chronic hyponatraemia is indicated by the absence or diminished severity of symptoms (Wynn & Rob, 1954; Arieff et al., 1976). This suggests that either the brain cells have adapted in some way to the increase in cell volume or that some mechanism has allowed the cell volume to return to normal. Arieff et al. (1976) have reviewed the evidence that in chronic water overload the osmolar and water content of the brain cells gradually fall. If this happened, then even if the plasma and cell osmolality remained low the brain cell volume (and plasma AVP) would return towards normal and symptoms might become less severe or even disappear.

The changes within the system which can cause severe acute or chronic hyponatraemia include changes in the osmoreceptor responsiveness to plasma osmolality and the presence of non-osmolar stimuli to AVP secretion (Leaf, 1962). On the other hand, changes in the biological half-life of AVP or in the renal responsiveness to AVP do not cause severe hyponatraemia because they can be compensated for by a change of AVP secretion (or thirst), which requires only a small change in plasma osmolality.

Acute clinical problems

Acute water overload with acute hyponatraemia only happens when a defect in the system reduces the patient's ability to excrete water. When a healthy person is given large volumes of water and injected with antidiuretic hormone (Stormont & Waterhouse, 1961) water is retained, the plasma osmolality and plasma sodium concentration fall, and the person develops headache and fatigue progressing to cramps, nausea, vomiting, diarrhoea and delirium. Acute water overload has also been produced in some women given large doses of Syntocinon intravenously in glucose solution (Morgan, Kirwan, Hancock, Robinson, Howe & Ahmad, 1977), and in these patients, as in others with acute water overload, the symptoms can progress to convulsions, unconsciousness and even death. There is some relationship between the amount of water retained, the magnitude of the fall in plasma sodium concentration and the presence and severity of symptoms (Swales, 1975; Arieff et al., 1976; Morgan et al., 1977). Acute severe hyponatraemia (less than 120 mmol/l, which is an average fall of 20 mmol/l) is probably always associated with symptoms (Arieff et al., 1976; De Troyer & Demanet, 1976).

There are many acute clinical situations where AVP secretion is sustained, in spite of a progressive fall of plasma osmolality, so that there must be a non-osmotic stimulus to AVP secretion. This happens after surgery, and when these patients are given solutions with a high water to sodium ratio the urine osmolality is too high for water balance (Thomas & Morgan, 1979), water is retained and
plasma osmolality and sodium concentration fall. Other non-osmotic stimuli to AVP secretion include ‘volume depletion’, low blood pressure (Robertson et al., 1976) and fainting (Davies, Slater, Forsling & Payne, 1976). Acute excessive AVP secretion is also present in patients with hyponatraemia and chest infection (Thomas et al., 1978) and may account for the hyponatraemia of glucocorticoid deficiency (Boykin, De Torrente, Erickson, Robertson & Schrier, 1978).

Where there is a non-osmotic stimulus to AVP and also in patients given Syntocinon, the presence and magnitude of the water retention (and thus of hyponatraemia) will of course depend on the water intake (or composition of intravenous fluids) as well as on the magnitude of the defect in the system, and the excess of AVP.

The excessive AVP secretion produced by a progressive fall in extracellular fluid volume has been discussed in terms of the priorities of maintaining osmolality and extracellular fluid volume. Osmolality is said to have the top priority at first during progressive volume depletion, and is then sacrificed as water is retained through an increased secretion of AVP, which minimizes the further fall in extracellular fluid volume. There is some doubt about the first part of this response (Brennan & Malvin, 1977; Weitzmann, Farnsworth, MacPhee, Che Ching Wong & Bennett, 1978), but volume deficits of more than 10–15% are, on average, associated with increased plasma AVP (Robertson et al., 1976). The response may vary greatly between persons so that some allow osmolality to fall from the beginning of volume depletion, and others maintain it until volume depletion is extreme (Morgan, Ball, Thomas & Lee, 1978). The stimulus to AVP secretion in volume depletion may be stimulation of volume receptors in the left atrium and the same mechanism might explain the sustained AVP secretion in patients with chest infections. A minority of patients taking diuretics develop hyponatraemia (Fichman, Vorherr, Kleeman & Telfer, 1971; Ghose, 1975; Kennedy, Mitchel & Hofford, 1978). The hyponatraemia is unlikely to be due to a movement of sodium into the cells (Alam, Wheeler, Wilkinson, Poston, Golindano & Williams, 1978) and it may be that it happens in those persons who retain water even when the volume (saline) depletion is small. Acute hyponatraemia may also arise because of a limit to urine flow, due to acute or chronic renal failure or an increased reabsorption of sodium in the proximal tubules, due to, for example, saline depletion. The acute hyponatraemia of beer drinkers is probably due to a combination of a large water intake and a limit to urine flow due to saline depletion (Demanet, Bonnyns, Bleiberg & Stevens-Rochmans, 1971).

The clinical effects of acute gross water over-load, as in the case of Syntocinon treatment, are dramatic and easily detected. The symptoms are easily missed in other situations where the symptoms are less dramatic, vague and non-specific, and can be attributed to the patient’s illness (Wynn & Rob, 1954). When symptoms have been sought in patients with hyponatraemia they have frequently been present, although non-specific (Arieff et al., 1976: Kennedy et al., 1978).

**Chronic clinical problems**

Chronic hyponatraemia has many causes and is common (Flear & Singh, 1973), but its physiological basis, clinical effects and significance for clinical management are less well defined than for acute water overload and hyponatraemia. As we have emphasized, the patients must be in a steady state, and are often free of symptoms.

There are several possible primary changes within the system which can lead to chronic hyponatraemia. One type of change is an ectopic production of AVP (as from a carcinoma of the lung). Such production should be uncontrolled (but, see Padfield, Morton, Brown, Lever, Robertson, Wood & Fox, 1976). There may be few chronic symptoms, but the patient may present with acute confusion, convulsions and coma, perhaps due to a sudden change in water intake, plasma osmolality and brain cell volume. However, chronic hyponatraemia with lowered plasma osmolality is much more commonly associated with a variety of conditions such as heart failure, various neurological disorders, hypothyroidism and drugs, particularly chlorpropamide and carbemazapine (Moses & Miller, 1974). In these conditions, AVP secretion continues in response to a non-osmolar drive such as volume depletion (when the plasma AVP may be normal or raised) or a lower setting or threshold of the osmoreceptor (when the plasma AVP would be normal). When there is a non-osmolar drive to AVP secretion the normal feedback system should be switched off, and there should be an excessive reduction in the plasma osmolality after a water load. In the case of resetting, the patient’s response to a water load should be normal, and this has been demonstrated in a few patients (DeFronzo, Goldberg & Zalman, 1976).
Robertson et al. (1976) have attempted to identify and distinguish some of these mechanisms of chronic hyponatraemia on the basis of the relationship between plasma AVP and plasma sodium, before and during an infusion of hyperosmolar saline.

The chronic hyponatraemia of heart failure is usually attributed to excess AVP due to volume depletion (Leaf, 1974; Swales, 1975), but it probably has several mechanisms (Takasu, Lasker & Shalhoub, 1961). In hypothyroidism the plasma AVP is greatly increased, even if there is little fall in the plasma sodium (Skowsky & Kikuchi, 1978). This raised plasma AVP may be due to an increased half-life of AVP, but the presence of a normal plasma sodium in some patients indicates a change in osmoreceptor setting and the presence of a steady state indicates a diminished renal responsiveness to AVP. Reduced renal responsiveness is observed in patients with other causes of hyponatraemia, and is therefore probably a secondary phenomenon (Leaf, 1962).

A change in renal function leading to an absolute limit in water excretion cannot be the cause of chronic hyponatraemia as a steady state cannot be achieved.

There is a view that in some patients the chronic hyponatraemia is due to ‘sick cells’. This is a controversial subject and the writings on it are made difficult by a lack of clear definitions. The general concept is that changes in cell function can cause the cells to gain sodium and lose potassium and lead to hyponatraemia. Three separate cell events may be involved: an increase in membrane permeability, a decreased activity of the sodium pump and a decrease of cell molecules. Flear & Singh (1973) suggested that an acute increase in cell permeability allows certain molecules to leave the cells and accumulate in the extracellular fluid. Retention of water will lead to a normal plasma osmolality and acute hyponatraemia. This combination is observed in some very ill patients after surgery or burns (Flear & Singh, 1973; Tindall & Clark, 1976) but has not been detected in patients with chronic hyponatraemia and heart failure (Leaf, 1974). Diminished activity of the sodium pump will cause the cells to gain sodium and lose potassium, but will not necessarily cause hyponatraemia (Flear & Singh, 1973; Swales, 1975).

The type of ‘sick cells’ which might be relevant to chronic hyponatraemia would be produced by a reduction in cell molecules, due to increased loss of diminished production (Flear & Singh, 1973). In the new steady state, there would be a normal cell volume but a low cell and plasma osmolality. The plasma AVP would be the same as in healthy people and would be what was expected for the cell volume, although it would appear excessive when related to the plasma sodium and plasma osmolality. There would be a normal response to variation in water intake. This form of ‘sick cells’ would therefore cause ‘resetting’ of the system, which was the functional change detected by Robertson et al. (1976) in a third of their patients with chronic hyponatraemia. In clinical practice it is difficult to distinguish between a primary reduction in cell molecules (‘sick cells’), an excessive secretion of AVP (from volume depletion) and an intrinsic failure of urinary dilution as the cause of the chronic hyponatraemia in conditions such as heart failure. The major theoretical difference is in the response of the system to a change in plasma osmolality, which should be normal if the cause is ‘sick cells’. Leaf (1962, 1974) excludes ‘sick cells’ and resetting as the cause of the chronic hyponatraemia of heart failure, because his patients were unable to excrete a water load normally. However, even when the primary event is an excess of antidiuretic hormone, the fall in plasma sodium is sometimes more than expected from the water retention alone (Morgan et al., 1977), so that water-loaded cells may become ‘sick cells’. There may therefore be more than one cause of hyponatraemia in the individual, and at least in heart failure the dominating cause may be different in different patients.

For these and other reasons, it has been suggested that the term inappropriate secretion of ADH should be abandoned (Swales, 1975; Thomas et al., 1978), and a simpler descriptive terminology, such as hyponatraemia of heart failure, should be used until the pathophysiology of the condition in general and in the individual has been clearly defined.

An alternative view of the system

We suggest that the physiological and clinical observations indicate that the system which is usually described as a system for water balance or osmolality control can more correctly and usefully be regarded as a system to control cell volume, particularly the volume of brain cells (Flear & Singh, 1973; Leaf, 1974).

An overall view of ‘fluid and electrolyte balance’ is that there are systems which separately set and regulate extracellular fluid volume and intracellular volume. The extracellular fluid volume is
set and regulated through the mechanisms which regulate total body sodium, which remains extracellular and at a particular osmolality determines extracellular fluid volume. The intracellular volume is set by pumping sodium out of cells to counter the volume-expanding effects of the cell molecules (MacKnight & Leaf, 1977), but is regulated acutely through changes in total body water and in chronic disease at least in part through changes in the cell molecules.

Pathophysiology of the system

The major clinical effects of a relative water overload and depletion are probably due to changes in brain cell volume. Unfortunately, the clinical effects such as headache, confusion and irritability are ill-defined, non-specific, difficult to quantify, even crudely, and are often ignored in ill patients. What is required is some measure or index of cell volume.

Changes in cell volume will be associated with changes in plasma osmolality and sodium. However, a fall in plasma sodium concentration can happen without a fall in plasma osmolality when there is an accumulation of lipids or proteins or an accumulation of molecules other than sodium, such as glucose or urea, or intracellular molecules which have leaked into the extracellular fluid (Flear & Singh, 1973).

Chronic hyponatraemia without symptoms could be due to a primary increase in AVP secretion with a secondary reduction in cell molecules and a normal cell volume, or to a primary reduction in cell molecules with a normal cell volume ('sick cells'). In both cases the cell volume is normal and treatment designed to remove water from the cell (which is, of course, the correct treatment in acute water overload with symptoms) would reduce the cell volume below normal and the patients would become ill (Thomas et al., 1978). The difference between these two causes of chronic hyponatraemia is that the patient with a primary increase in AVP secretion is unable to respond to an increase in water intake, and is liable to acute water overload with symptomatic acute or chronic hyponatraemia with symptoms. The symptoms would presumably disappear when the plasma sodium increased to its previous low value and to raise it to a normal concentration would be to make the patient ill.

References


