Severe hyponatraemia: Current concepts on pathogenesis and treatment

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ABSTRACT
Severe hyponatraemia (serum sodium <120 mEq/L) is a serious electrolyte disorder associated with life-threatening neurological complications. It develops most often when the ability of the kidney to excrete free water is impaired. The initial adaptation of the brain to hyponatraemia includes loss of water, sodium, potassium and chloride into the cerebrospinal fluid and the late adaptation consists of the loss of organic osmolytes. Adaptation of the brain to hyponatraemia causes potential problems during therapy, as re-adaptation requires a considerably longer time. Rapid correction of hyponatraemia may lead to the development of the osmotic demyelination syndrome. Though the ideal treatment for severe hyponatraemia remains controversial, a consensus regarding therapeutic guidelines has emerged. The rate of correction and the type of infusate depend on the duration and cause of the hyponatraemia, clinical presentation, volume status, renal function and the serum potassium level. The prognosis of the osmotic demyelination syndrome is rather dismal although several therapeutic modalities have been tried.

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INTRODUCTION
Hyponatraemia is the most frequent electrolyte disorder observed in general medical practice. In almost all cases, it is due to an excess of water rather than sodium depletion. The majority of instances, hyponatraemia is mild and patients are asymptomatic. However, severe hyponatraemia, arbitrarily defined as a serum sodium concentration <120 mEq/L, is a serious electrolyte disorder which exposes patients to the risk of developing major neurological complications. Uncorrected severe hyponatraemia produces cerebral oedema, an increased intracranial pressure and may cause tentorial herniation. On the other hand, rapid or over-correction of hyponatraemia could lead to the development of demyelinating lesions and permanent neurological damage. In the past few years, considerable advances in the field of brain physiology and various brain adaptive mechanisms have improved our understanding of the neurological events associated with hyponatraemia. Though the ideal treatment for hyponatraemia is still debated, a consensus regarding the therapeutic guidelines has emerged.

PATHOGENESIS
Hyponatraemia develops most often due to the retention of excess water rather than sodium depletion. It is either a result of ingestion of water beyond the maximal excretory capacity of the kidney or when water excretion by the kidney is impaired, even with consumption of lesser amounts of water. In an individual who consumes 4 g of salt and 70 g of protein (700 mOsm solute/day), at minimal urinary concentration (50 mOsm/kg) the maximal urine volume possible is 14 L/day (700/50=14). Hyponatraemia would develop if the daily fluid intake exceeds this limit. This situation, although rare, can occur due to compulsive water drinking in the setting of a severe psychiatric illness. This condition is called primary polydipsia and most patients who have this disorder suffer from schizophrenia.

Severe hyponatraemia can also be induced with an acute waterload of 3-4 L. This has been reported in anxious patients waiting for a radiological examination or urine testing. In most instances, hyponatraemia occurs as a result of reduced renal free water clearance. The kidney is able to generate free water only if all of the following conditions are satisfied: 1. Delivery of salt and water to the thick ascending limb of the loop of Henle must be intact. This requires an adequate renal plasma flow (RPF) and glomerular filtration rate (GFR) as well as an adequate delivery of salt and water out of the proximal convoluted tubule. 2. The thick ascending limb of the loop of Henle must be intact so that sodium can be removed without water. 3. Antidiuretic hormone (ADH) must be suppressed so that the collecting ducts do not reabsorb the water generated in the proximal segments. A defect involving any of the above could result in hyponatraemia. The important causes of severe hyponatraemia and its pathogenesis in each of the conditions are discussed later. Hyponatraemia caused by hyperglycaemia, and pseudohyponatraemia seen in hyperlipidaemia and paraproteinaemia are virtually never severe.

Syndrome of inappropriate ADH secretion and cerebral salt-wasting syndrome
The syndrome of inappropriate ADH secretion (SIADH) is characterized by primary water retention induced by excessive ADH for the level of plasma osmolality. Inappropriate ADH release due to any cause produces hyponatraemia by interfering with urinary dilution and preventing the excretion of ingested water. The ADH increases water reabsorption predominantly in the collecting ducts by increasing the expression of aquaporin-2. Various central ner-
vous system disorders including stroke, infection, trauma and psychosis can enhance ADH release. The other important causes of SIADH include vasopressin-producing tumours, pulmonary diseases such as pneumonia and tuberculosis, and a variety of drugs. The common neoplasms reported to cause SIADH include small cell carcinoma of the lung and cancer of the pancreas and duodenum. Drugs which enhance ADH release or its effect include chlorpropamide, carbamazepine, cyclophosphamide and vincristine.

In SIADH, overt signs of hypervolaemia do not accompany water retention as only one-third of the water is distributed in the extracellular space. However, a modest expansion of intravascular volume results in an increased RPF and GFR. Volume expansion results in reduced proximal tubular absorption of sodium, and the plasma concentration of substances (uric acid and urea) that are reabsorbed along with sodium in the proximal convoluted tubule also tend to be reduced. Once a steady state is reached, urinary sodium excretion becomes equal to the dietary sodium intake.

Cerebral salt-wasting syndrome (CSWS) is relatively rare and is described in patients with cerebral disease. It is characterized by severe renal salt wasting, hyponatraemia and volume depletion, in contrast to SIADH in which there is euvoalma. Other differences between the two disorders are given in Table II. The aetiology of this disorder is not clear. It has been postulated that the release of a natriuretic peptide (brain natriuretic peptide) by the hormone-producing neurones in the brain is largely responsible for the natriuresis.

### Postoperative hyponatraemia

The development of postoperative hyponatraemia is attributed to the two factors: (i) infusion of excessive amounts of hypotonic fluids such as dextrose and hypotonic saline in the acute postoperative period; and (ii) a high level of ADH in the postoperative period due to pain, nausea, anxiety, stress and drugs such as morphine, which prevent the excretion of electrolyte-free water. Under the influence of ADH, the urine becomes hypertonic and administration of even isotonic fluids may result in hyponatraemia. The entire amount of sodium in 2 L of isotonic saline (300 mmol) can be excreted in 1 L of hypertonic urine, leading to a positive balance of 1 L of electrolyte-free water in the body resulting in hyponatraemia. This process is equivalent to ‘desalination’ of 2 L of isotonic saline.

### Severe renal failure

Hyponatraemia can occur in both acute and chronic renal failure. Patients with severe renal failure have a relative inability to excrete free water. In such patients, the minimum urine osmolality may be reduced to 200–250 mOsm/kg, despite appropriate suppression of ADH. Fluid intake exceeding the maximum diluting capacity of the kidney will result in hyponatraemia.

### Diuretic-induced hyponatraemia

Almost all cases of diuretic-induced hyponatraemia are due to thiazide diuretics and not loop diuretics. Thiazides act exclusively in the distal tubule and do not interfere with urinary concentration or the ability of ADH to promote water retention. Further, the use of thiazide diuretics results in the loss of effective solutes (Na⁺ and K⁺) in excess of water. Diuretic-induced volume depletion, which results in impaired water excretion due to enhanced ADH release, and decreased fluid delivery into the diluting segment also contribute to hyponatraemia.

### Endocrine disorders

Hypothyroidism, hypoadrenalism and glucocorticoid deficiency occurring as a result of hypopituitarism may interfere with the excretion of free water resulting in hyponatraemia. In all these conditions water retention is predominantly ADH dependent. Hyponatraemia in primary adrenal deficiency is related to both hypocortisolism and hypoaldosteronism. However, severe hyponatraemia is unusual in isolated hypoaldosteronism as other hormones such as angiotensin II and norepinephrine may compensate for aldosterone deficiency. Hyperscretion of ADH in hypocortisolism may be related to a reduction in blood pressure and cardiac output which is induced by a deficiency of cortisol. In addition, ADH secretion may be directly stimulated by corticotropic-releasing hormone (CRH) from the paraventricular nuclei of the hypothalamus. Antidiuretic hormone is an adrenocorticotropic hormone (ACTH) secretagogue, and cortisol deficiency leads to stimulation of CRH secretion and thus ADH production.

### Congestive heart failure (CCF) and cirrhosis of the liver

Hyponatraemia in CCF is due to the relative inability of the kidney to excrete ingested water. A fall in the cardiac output and mean arterial blood pressure stimulates the secretion of ADH, renin–angiotensin and norepinephrine. Angiotensin and norepinephrine limit the distal water delivery by reducing the renal perfusion and GFR. Antidiuretic hormone prevents the excretion of free water in the collecting tubules. Angiotensin II is also a potent stimulus for thirst, leading to increased water intake. As in CCF, hyponatraemia due to liver disease is a consequence of the inability to excrete ingested water. In CCF and cirrhosis, hyponatraemia is often mild, but it can be severe and its degree depends on the severity of the primary disorder.
Hyponatraemia due to reduced solute intake

Occasionally, decreased solute intake may also lead to severe hyponatraemia. Though uncommon, this situation can occur in elderly individuals with poor dietary intake and in those who ingest 4–5 L of fluids as beer (beer potomania) and consume very little food.39 Even though such individuals excrete maximally dilute urine, the total amount of urine that can be formed is reduced by the limited amount of solutes (sodium, potassium, chloride, and urea) in the urine. If the daily dietary solute intake is reduced from 700 mOsm to 150 mOsm, even with minimal urinary concentration (50 mOsm/kg), the maximum volume of urine that can be formed daily will be reduced from 14 L to 3 L (150/50 = 3). If the daily fluid intake exceeds this amount hyponatraemia would ensue.

Brain adaptation to hyponatraemia

Soon after the development of hyponatraemia, the following sequence of events occurs. The brain cells exposed to hypertonic plasma swell as a result of osmotic fluid shifts into the brain. As the swelling occurs inside the rigid confines of the skull, it may lead to a reduction in the cerebral blood flow.

The early adaptation of the brain to hyponatraemia-mediated oedema is by loss of water into the cerebrospinal fluid (CSF). The initial cerebral oedema elevates the interstitial pressure, creating a gradient for extracellular fluid movement out of the brain and into the CSF. This is followed by extrusion of sodium, potassium and organic osmolytes from the brain cells.40,41 The movement of electrolytes occurs quickly, as it is mediated by the activation of quiescent cation channels in the cell membrane. Organic solute loss occurs later because it requires the synthesis of new transporters.42 The major osmolytes lost from the brain cells are myo-inositol, glycerophosphatyl choline, glutamate, glutamine, creatinine and taurine.41,42 Organic osmolytes account for approximately one-third of the solute loss in chronic hyponatraemia. Most of the adaptation is achieved within 48–72 hours of sustained hyponatraemia. The information about the adaptation of the brain has been derived largely from animal experiments; however, studies in patients with chronic hyponatraemia using regional quantitative proton magnetic resonance spectroscopy have confirmed these findings43 (Fig. 1).

If adaptation of the brain is incomplete, increased intracranial tension develops leading to a marked reduction in cerebral blood flow and CSF production. If hyponatraemia is not corrected, oedema continues to increase with eventual tentorial herniation and cerebral ischaemia.

Young menstruating women are at a greater risk for developing severe hyponatraemic symptoms and at a much greater risk (25-fold compared to men) of developing residual neurological deficits.44,45 These gender-related effects may be mediated through the actions of female sex hormones. Oestrogens have been found to stimulate vasopressin release and antagonize the various mechanisms for adaptation of the brain which occur following the development of hyponatraemia.46 Other risk factors for developing severe hyponatraemic encephalopathy are given in Table III.

Osmotic demyelination. The adaptation that returns brain volume to normal and protects against the development of cerebral oedema creates a potential problem for therapy.47,48 A rapid increase in the plasma sodium concentration can lead to the osmotic demyelination syndrome (also called central pontine myelinolysis).4,6 The exact mechanism by which rapid correction of hyponatraemia results in myelinolysis has not been clearly elucidated. Chronic hyponatraemia is associated with loss of cerebral osmolytes, and correction of hyponatraemia requires a re-adaptation of the brain cells to re-accumulate the osmolytes lost during adaptation.42 Apparently, these re-adaptation events require more time than adaptation to hypo-osmolality. As a result, during correction of hyponatraemia, the brain cells become hypertonic to the extracellular fluid, and water is drawn from the brain cells and the brain volume shrinks. Further, the levels of sodium and chloride in the brain overshoot the normal range.49 During re-adaptation, there is a delay in the re-accumulation of organic osmolytes, as transport of these osmolytes requires synthesis of new transporters.42,47 Studies on rats have shown that re-accumulation of inorganic ions was complete within 24 hours, while restoration of organic osmolytes required 5–7 days.49,50 High concentrations of cerebral inorganic ions in the absence of adequate concentrations of organic osmolytes could have a role in the pathogenesis of myelinolysis.51 The areas affected by myelinolysis share an intermix of neurones, myelinated fibres and oligodendroglia.

It has been suggested that differential swelling and shrinkage of various cellular elements results in compression of myelinated fibres and subsequent demyelination.52,53 Other researchers have suggested that an increased number of oligodendrocytes in perifascicular distribution as opposed to interfascicular distribution account for the vulnerability of the pons and other areas to osmotic stress.54 The risk factors for developing osmotic demyelination syndrome are given in Table III.

CLINICAL PRESENTATION

The clinical manifestations of hyponatraemia are related to the neurological dysfunction caused by cerebral oedema.3,55 Nausea and malaise are the earliest symptoms followed by headache, lethargy and mental obtundation.3,55 In severe cases, death can result from tentorial herniation and brainstem compression. The

![Fig 1. Brain adaptation following hyponatraemia](image)

ICF intracellular fluid ISF interstitial fluid CSF cerebrospinal fluid

| Table III. Hyponatraemic patients at risk of developing neurological complications |
|---------------------------------|-------------------|
| **Acute cerebral oedema** | **Osmotic demyelination syndrome** |
| Young menstruating women | Alcoholics |
| Elderly women on thiazides | Malnourished patients |
| Children | Hypokalaemic patients |
| Psychiatric polydipsic patients | Burn victims |
| Hypoaemic patients | Elderly women on thiazide diuretics |
| | Liver transplant recipients |
mortality and morbidity correlate more with the rate of decrease of plasma sodium than the actual magnitude of reduction.

In acute severe hyponatraemia (duration <48 hours), encephalopathy is usually present, whereas in chronic severe hyponatraemia (duration >48 hours) patients may be asymptomatic due to efficient brain adaptive mechanisms. Hypoxia could aggravate the brain injury due to hyponatraemia; it could also act as a co-morbid factor by impairing the adaptation of the brain through inhibition of sodium transport.

The clinical manifestations of osmotic demyelination may be delayed for 2–6 days after the elevation of serum sodium and include dysarthria, dysphagia, paraparesis or quadriaparesis and rarely, even seizures or coma. The size of the lesions does not correlate with the severity of neurological illness and patients with large demyelinating lesions may be asymptomatic. Computerized tomographic (CT) scanning frequently fails to detect myelinolytic lesions seen at autopsy. Demyelinating lesions can be detected by magnetic resonance imaging (MRI), and appear as areas of increased signal activity on T₂-weighted scans and as areas of decreased signal activity on T₁-weighted MRI scans (Fig. 2).

**DIAGNOSTIC APPROACH**

This involves the assessment of the extracellular fluid volume status, measurement of renal function, serum uric acid and urinary sodium (Fig. 3). Both SIADH and CSWS are characterized by hypouricaemia; restoration of normonatraemia will result in normalization of uric acid levels in SIADH but in CSWS hypouricaemia will persist.

**TREATMENT**

The optimal treatment of hyponatraemia has been a matter of debate. Controversy exists regarding the rate at which the sodium level should be corrected. Rapid correction could cause cerebral demyelination while slow correction would result in the detrimental effects of persistent hyponatraemia. Some authors advocate a rapid correction with a final target of 130 mEq/L, but the correction must not exceed 25 mEq/L in 48 hours. These investigators are of the opinion that cerebral demyelinating lesions develop only in patients with stable hyponatraemia, who are inadvertently made hypovoltaemic during treatment or if the absolute increase in plasma sodium exceeds 25 mEq/L in the first 24–48 hours of treatment. Others recommend a more conservative approach, suggesting a correction of 0.5 mEq/L/hour and a maximum increase in serum sodium of 12 mEq/L or 18 mEq/L in 48 hours. However, it should be emphasized that although most reported cases of osmotic demyelination occurred when the rate of correction exceeded 12 mEq/L per day, demyelination could occur with a rate of correction as low as 9 mEq/L per day.

The rate at which plasma sodium should be corrected depends on the clinical presentation and duration of hyponatraemia (Fig. 4).

**Acute severe symptomatic hyponatraemia (duration <48 hours)**

This condition typically develops in hospitalized patients receiving hypotonic intravenous (i.v.) fluids. Prompt correction is re-
Estimation of water excess and sodium (solute) requirement

Excess water exceeds 20 mEq in the first 48 hours, especially in those patients who have had hyperglycemia or a hepatic impairment suggestive of osmotic demyelination (Table III). Correction should not exceed 20 mEq in the first 48 hours, especially in those patients with additional risk factors for osmotic demyelination. Correction to higher than normal serum sodium concentration should also be avoided.

Treatment overshoot. This may occur despite careful monitoring. If the patient remains asymptomatic, correction may be slowed or temporarily stopped. If there is any sign of brain impairment suggestive of osmotic demyelination, an infusion of 5% dextrose or administration of dDAVP may be required to lower the plasma sodium to a level at which symptoms improve or disappear.

Chronic severe symptomatic hyponatraemia

If the patient is symptomatic and the duration of hyponatraemia is uncertain, careful correction is needed. The primary problem in these patients is cerebral oedema and any delay in treatment is more dangerous than the potential consequences of rapid correction. Such patients require aggressive initial correction at a rate of 1–1.5 mEq/L/hour for the first few hours or until the symptoms resolve. However, plasma sodium should not be raised by more than 12 mEq/L over a period of 24 hours, as partial adaptation of the brain would have already occurred. Correction should not exceed 20 mEq in the first 48 hours, especially in those patients with additional risk factors for osmotic demyelination (Table III). Correction to higher than normal serum sodium concentration should also be avoided.

Treatment overshoot. This may occur despite careful monitoring. If the patient remains asymptomatic, correction may be slowed or temporarily stopped. If there is any sign of brain impairment suggestive of osmotic demyelination, an infusion of 5% dextrose or administration of dDAVP may be required to lower the plasma sodium to a level at which symptoms improve or disappear.

Chronic severe asymptomatic hyponatraemia

In this condition, patients are at little risk for neurological damage, as cerebral adaptation would already have occurred. Rapid correction is not indicated in them and could be harmful. The current recommendation is to raise the serum sodium level at a rate of 0.5 mEq/L/hour (less than 10 mEq/L/day). Fluid restriction and administration of oral salt can achieve this.

Estimation of water excess and sodium (solute) requirement

Apart from hyponatraemia associated with hypovolaemia, severe hyponatraemia is a disorder of excess water and treatment involves getting rid of the extra water. The following formula can be used to estimate the extra water that must be excreted to achieve an increment in the sodium serum level.

Excess water = Total body water – (actual serum Na⁺/desired serum Na⁺) × Total body water

Alternatively, the amount of sodium required for generating this water loss and hence to correct the hyponatraemia can be calculated by the formula given below:

Change in serum sodium = Infusate sodium – serum sodium
Total body water + 1

This formula estimates the effect of 1 L of any infusate on serum sodium. The objective of giving sodium is to provide an osmotic load so as to get rid of the excess water. The sodium concentration of commonly used infusates is given in Table IV. The estimated total body water (TBW) (in L) is calculated as a factor of body weight. Normal values for TBW are 0.5 and 0.6 times the lean body weight in women and men, respectively. If the electrolyte concentration of the infusate is higher than that of urinary electrolytes, the level of serum sodium will increase as a result of free water excretion. This formula is based on the assumption that no gain or loss of water or electrolytes other than the infusate occurs during the course of treatment. However, in actual practice, renal and extrarenal losses of water and electrolytes can be substantial and frequent monitoring of electrolytes and appropriate modification of fluid therapy are essential.

TREATMENT IN SPECIFIC CLINICAL SETTINGS

Treatment of hyponatraemia primarily involves correction of the serum sodium level. The mode of treatment including the type of fluid to be administered and the rate of correction would depend on the primary abnormality that has caused the disorder. The therapeutic approach should also be modified depending on the renal function and presence of other electrolyte abnormalities such as hypokalaemia.

Hyponatraemia due to SIADH

In severe hyponatraemia due to SIADH, if the serum sodium concentration has to be corrected, osmolality of the fluid administered must exceed that of the urine. In patients with SIADH, urine osmolality can be as high as 600 mOsm/kg. If normal saline is used to correct hyponatraemia, this will only result in a drop in the serum sodium level. This paradoxical response is due to the fact that 1 L of 0.9% NaCl contains only 300 mOsm of solutes (150 mEq each of Na⁺ and Cl⁻) which can be excreted in 500 ml of urine resulting in the retention of the remaining 500 ml of water and worsening of hyponatraemia. On the other hand, with hypertonic saline (3% NaCl), a greater quantity of solute (1026 mOsm; 513 mEq each of Na⁺ and Cl⁻) can be administered in a smaller quantity of water. The increased solute load will promote water excretion, eventually raising the sodium serum level. The effect of hypertonic saline can be further enhanced by the use of a loop diuretic such as furosemide.

In SIADH, the ADH levels are fixed and the main determinant of urine output is the solute intake. Hence, in chronic SIADH, increasing the daily solute intake can enhance water excretion. A diet with a high content of protein and salt can be recommended for this purpose.

Severe hyponatraemia in volume depletion

Hypovolaemic hyponatraemia should be corrected with isotonic saline. However, occasionally administration of isotonic saline in volume-depleted patients can result in overly rapid correction of hyponatraemia. Restoration of normovolaemia will remove the stimulus for ADH release and result in maximal water excretion, which may result in rapid correction of hyponatraemia. Hence, once diuresis starts half normal saline must be given.

Hyponatraemia with severe renal failure

Patients with severe renal failure and hyponatraemia who are dialysed against high-dialysate sodium can have an acute rise in serum sodium levels. These patients may be partially protected against osmotic demyelination, as the concurrent removal of urea will lower the plasma osmolality promoting water movement into the brain. The shift of water in the opposite direction will reduce the risk of cerebral contraction caused by a rise in serum sodium levels.

| TABLE IV. Sodium concentration of commonly used infusates |
|-----------------|-----------------|
| Infusate        | Infusate sodium (mEq/L) |
| 5% sodium chloride | 855               |
| 3% sodium chloride | 513               |
| 0.9% sodium chloride | 154               |
| 0.45% sodium chloride | 77                |
| Ringer lactate solution | 130               |
concentration. This has been shown in azotaemic rats made severely hyponatraemic by the administration of subcutaneous ADH and hypotonic fluids. Subsequent rapid correction of hyponatraemia was not associated with the development of osmotic demyelination. On the other hand, rapid correction of hyponatraemia in non-azotaemic rats was accompanied by the development of severe neurologic features suggestive of the osmotic demyelination syndrome. However, as a safety precaution most authorities would not recommend that the difference between the plasma sodium and dialysate sodium exceed 15–20 mEq/L.

**Hyponatraemia in the presence of hypokalaemia**

Administration of potassium can raise the serum sodium concentration and osmolality in a hyponatraemic patient. As most of the administered potassium goes into the cells, sodium moves into the extracellular fluid to maintain electroneutrality. In addition, movement of extracellular chloride into the cells along with potassium increases the intracellular osmolality, promoting free water entry into the cells. This relationship between sodium and potassium becomes important in patients with hyponatraemia and hypokalaemia, in whom administration of potassium will correct both disorders and giving additional sodium may lead to a rapid elevation in the serum sodium concentration.

**Hyponatraemia due to CSWS**

Distinguishing between SIADH and CSWS is of great importance with regard to the therapy. Administration of normal saline is indicated in patients with CSWS as the extracellular fluid volume is contracted due to renal salt wasting. Fludrocortisone, a synthetic aldosterone-like compound has been used to treat CSWS with varying degrees of success.

**Congestive heart failure and cirrhosis**

Severe hyponatraemia in CCF and cirrhosis is associated with a very poor prognosis. The severity of hyponatraemia parallels the severity of the primary disorder. Water restriction is the mainstay of treatment, although this is often difficult. Hyperonotic saline with high-dose furosemide may be used for patients who have symptomatic hyponatraemia. However, care has to be taken to prevent the development of osmotic demyelination. Vasopressin antagonists (specific for V2 receptors) can be tried to increase the free water clearance (discussed later).

**OTHER THERAPEUTIC OPTIONS**

The following therapeutic agents have been used alone or in combination with saline for correcting severe hyponatraemia. These agents work by enhancing the clearance of free water.

**Urea**

Urea has been proposed for the treatment of hyponatraemia for more than 15 years. A number of patients treated with urea achieved a correction level of >12 mEq/L/24 hours without any neurological sequelae. Urea induces water loss by providing an osmotic load. The mechanism by which urea prevents the development of lesions in the brain during the course of correction remains hypothetical. Urea diffuses into the brain and its accumulation prevents excessive brain dehydration. Urea could also trigger the accumulation of organic osmolytes in the brain. It is contraindicated for patients with renal failure and advanced liver disease.

**Demeclocycline and lithium**

Demeclocycline and lithium act on the collecting tubule reducing its responsiveness to ADH. Both drugs interfere with the generation and action of cyclic adenosine monophosphate, the intracellular mediator of ADH. These drugs can be considered for patients with persistent hyponatraemia unresponsive to water restriction, high salt intake and a loop diuretic. Demeclocycline is more effective and less toxic than lithium. A daily dose of 600–1200 mg would be effective in most patients. However, several side-effects have been reported with this drug including gastrointestinal disturbances, nephrotoxicity and photosensitivity.

**Vasopressin receptor antagonists**

ADH receptor antagonists that are selective for the V2 receptor may be beneficial in patients with SIADH, and in hyponatraemic patients with congestive heart failure and hepatic cirrhosis. These agents are currently undergoing phase III trials and will soon be available for clinical use. They increase the free water clearance and augment the correction of hyponatraemia.

**TREATMENT OF OSMOTIC DEMYELINATION SYNDROME**

Osmotic demyelination syndrome is associated with a dismal prognosis and no effective therapy has yet been discovered. Dexamethasone and colchicine have been used in experimental animals but no data from human studies are available. Aggressive plasmapheresis was tried in 3 patients immediately after the diagnosis; 2 patients had either no or clinically silent neurological deficits, while the third had only a mild neurological deficit. Recently, i.v. immunoglobulins at a dose of 400 mg/kg daily have been successfully used in a patient with diplopia and hemiparesis due to myelinolysis. Although these results are promising, a larger number of patients need to be studied to confirm the role of these therapeutic modalities.

**REFERENCES**


