Disturbances of Sodium in Critically Ill Adult Neurologic Patients

A Clinical Review

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Abstract: Disorders of sodium and water balance are common in critically ill adult neurologic patients. Normal aspects of sodium and water regulation are reviewed. The etiology of possible causes of sodium disturbance is discussed in both the general inpatient and the neurologic populations. Areas of importance are highlighted with regard to the differential diagnosis of sodium disturbance in neurologic patients, and management strategies are discussed. Specific discussions of the etiology, diagnosis, and management of cerebral salt wasting syndrome, the syndrome of inappropriate antidiuretic hormone secretion, and central diabetes insipidus are presented, as well as the problems of overtreatment. The importance of diagnosis at an early stage of these diseases is stressed, with a recommendation for conservative management of milder cases.

Key Words: hypernatremia, hyponatremia, cerebral salt wasting, syndrome of inappropriate antidiuretic hormone secretion, diabetes insipidus

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NORMAL PHYSIOLOGY OF SALT AND WATER REGULATION

Sodium is the major extracellular cation in the body and is therefore one of the most important osmotically active solutes. The extracellular to intracellular sodium concentration gradient is maintained by the cell membrane Na-K ATPase pump, and total body sodium is controlled via renal excretion. Sodium reabsorption occurs predominantly at the proximal convoluted tubule and is affected by sympathetic innervation, atrial natriuretic peptide (ANP), and brain natriuretic peptide (BNP). ANP is released from the cardiac atrium, whereas BNP is found in the brain and cardiac ventricle.[1] ANP and BNP cause natriuresis via a direct effect on the inner medullary collecting duct as well as inhibiting renin and aldosterone release.[2] C-type natriuretic peptide and dendroaspis natriuretic peptide may also be implicated in sodium regulation.[3]

Total body water volume is predominantly controlled by renal manipulation of body sodium, with resulting water volume adjustment to maintain tonicity. Water makes up 60% of the mass of the human body and moves freely between intracellular and extracellular fluid spaces as dictated by the movements of osmotically active particles. Water balance is monitored by osmoreceptors in the hypothalamus, low pressure baroreceptors located in the right atrium and great veins, and high pressure baroreceptors in the carotid sinus. The two main mechanisms for controlling water balance are antidiuretic hormone (ADH) secretion and thirst. Increases in extracellular fluid (ECF) tonicity cause secretion of ADH from the posterior pituitary, promoting free water reabsorption in the kidney, leading to concentrated urine. Hypovolemia is also a potent stimulus for ADH release via the renin–angiotensin–aldosterone system. For example, the hypo-osmolar state of sodium depletion will result in low plasma volume as a homeostatic response to maintain osmolality, and the hypo-osmolar state of water retention will promote sodium loss for water offloading. Sodium loss from the kidneys or gastrointestinal tract may therefore promote a diuresis, but the resulting low plasma volume causes activation of the renin–angiotensin–aldosterone system, promoting net reabsorption of sodium, and water retention.

Changes in sodium and water balance have a profound effect on the brain and central nervous system (CNS), and the behavior of the brain cell in response to changing plasma osmolality has previously been described.[4] In acute hyperosmolar states, there is loss of intracellular water with cell shrinkage followed by gradual restoration of brain volume via the generation of nonelectrolyte osmotically active intracellular solute. In the hypo-osmolar state, there is cellular expansion, which is corrected over time by the loss of intracellular solute. Total brain volume is therefore preserved by alterations in the intracellular milieu.

DYSNATREMIA

Disturbance of sodium balance, referred to as dysnatremia in this review, is a frequent finding in adults in the hospital in-patient setting[5] and accounts for the bulk of electrolyte disturbances in this patient population.[6] The symptoms and signs of sodium disturbance are related to the balance between sodium and water balance and are shown in Table 1.

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TABLE 1. Symptoms and Signs of Hypo- and Hypernatremia

	Moderate	Severe
Hyponatremia	Lethargy	Drowsiness/confusion
	Nausea/vomiting	Depressed reflexes
	Irritability	Seizures
	Headache	Coma
	Muscle weakness/cramps	Death
Hypernatremia	Lethargy	Hyperreflexia
	Thirst	Ataxia
	Irritability	Seizures
		Coma

This review will focus on dysnatremia in the adult neurologic patient, but within the context of sodium disturbance in the in-patient general hospital population.

HYPONATREMIA

Epidemiology

The reported incidence of hyponatremia depends on its threshold for diagnosis, but is usually defined as serum sodium <135 mmol/L. Hyponatremia has been reported in 1%–15% of hospital inpatients[7–9] and is associated with a mortality increase of 7%–60%.[8] Furthermore, acute hyponatremia leads to greater mortality than chronic states.[10] Hyponatremia is more common in neurologic patients than in the general hospital population[11] and is particularly associated with aneurismal subarachnoid hemorrhage (SAH),[12] traumatic brain injury (TBI),[13] and basilar meningitis.[14]

Causes

The causes of hyponatremia are numerous (Table 2), but in the adult neurologic patient population, hyponatremia most commonly occurs because of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or the cerebral salt wasting syndrome (CSWS). In addition to pathologic causes, administration of hypotonic fluid is a common iatrogenic cause of hyponatremia in hospitalized patients.[5,7] Hyponatremia has also been noted in patients receiving normal saline as maintenance fluid,[15] and this may occur because of perioperative ADH secretion, as a stress response. It is important to remember that hyponatremia can occur in the setting of hypo-, eu-, or hypervolemia, and the causes of hyponatremia may be distinguished by the associated volume disturbance.

TABLE 2. Common Causes of Hyponatremia

Decreased ECF Volume
- Extrarenal sodium loss
  - Diarrhea
  - Vomiting
  - Blood loss
  - Excessive sweating
- Intrarenal sodium loss
  - Cerebral salt wasting syndrome
  - Diuretics
  - Osmotic diuresis
  - Adrenal insufficiency
  - Ketonuria

Normal ECF Volume
- Syndrome of inappropriate ADH secretion
  - CNS
    - Space-occupying lesions
    - Trauma
    - Hemorrhage
    - Stroke
    - Inflammatory disorders
    - Demyelination
  - Drugs
    - Carbamazepine
    - Chlopropramide
    - Oxcarbazepine
    - Phenothiazines
    - Serotonin reuptake inhibitors
    - Tricylic antidepressants
    - Vincristine
  - Pulmonary conditions
    - Infection
    - Acute lung injury
    - Neoplasia
- Thiazide diuretics
- Adrenal insufficiency
- Hypothyroidism
- Primary polydipsia

Increased ECF Volume
- Congestive cardiac failure
- Nephrotic syndrome
- Renal failure
- Cirrhosis

Syndrome of Inappropriate Antidiuretic Hormone Secretion

SIADH was first described by Schwartz in 1957 in patients with bronchogenic carcinoma.[16] The key findings were urinary sodium loss without corresponding loss of water, leading to a decrease in plasma osmolality in the presence of hypertonic urine. Treatment by fluid restriction led to resolution of these abnormalities.

The pathophysiology of SIADH is not fully understood, although ADH release correlates with a change in the threshold for the thirst response, with a lower threshold for thirst in patients with SIADH.[17] However, there is also loss of control of ADH release, with plasma ADH levels being unchanged by drinking[17] or by osmotic stimulus.[18]

SIADH is associated with many conditions, and these are best classified into four major categories: neoplasia, nonmalignant lung disease, drugs, and neurologic diseases. The most common causes in the neurologic group include meningitis/encephalitis, brain tumor, SAH, and TBI. SIADH has also been reported following spinal surgery.[19] Drug-related hyponatremia secondary to the antiepileptic drugs carbamazepine and oxcarbazepine is of particular relevance in the care of neurologic patients. The etiology of hyponatremia has recently been reviewed in detail elsewhere.[9]

Cerebral Salt Wasting Syndrome

CSWS, a syndrome characterized by polyuria and natriuresis, was first described by Peters in 1950[20] and was subsequently ascribed to disruption of hypothalamic–renal pathways.[21] A current working definition of CSWS is renal loss of sodium due to intracranial disease, leading to hyponatremia and hypovolemia. Whereas the pathophysiology of CSWS is not fully understood, the evidence suggests that raised levels of circulating ANP and BNP mediate, at least in part, increased natriuresis and hyponatremia in acute brain injury, especially after SAH.[22] There is an initial elevation of ANP following SAH, but ANP levels subsequently fall and the initial rise is not correlated with hyponatremia.[23] An increased ANP level has also been reported as a normal response to trauma, and this cannot be suppressed with correction of volume status.[24] Elevated BNP levels are also associated with hyponatremia, and plasma levels have been correlated with urinary sodium excretion and intracranial pressure.[25]

CSWS is predominantly associated with SAH but has also been described in conjunction with TBI, glioma, and tuberculous or carcinomatous meningitis.[22]

Investigation of Hyponatremic Neurologic Patient

Except in life-threatening disturbances of sodium homeostasis, the initial finding of an abnormal sodium level should always prompt specific investigation into the underlying cause before management is initiated. The speed of onset of the hyponatremia, as well as the presence of symptoms, is most important because patients with the most rapid onset are more likely to become symptomatic.[26] A differentiation must be made between hypervolemia with normal total body sodium (suggesting SIADH) and hypovolemia with disproportionately low total body sodium (suggesting CSWS). This differentiation is crucial because the managements of these two conditions are diametrically opposed.[27,28]

The diagnostic criteria of SIADH were summarized by Harrigan in 1996[29] and are shown in Table 3. Although these criteria are adequate in the presence of an appropriate level of clinical suspicion, other diagnostic tests for SIADH have been described, including measurement of elevated levels of plasma and/or urinary ADH levels.[30,31] Attempts have been made to identify derived parameters of sodium and water homeostasis for the differentiation between SIADH and CSWS to avoid the need to measure total body water and circulating blood volume.[32] In SIADH, there is high free water absorption, low fractional water and sodium excretion, low or normal urine output, and increased ADH, whereas in CSWS, there is normal free water absorption, increased fractional water and sodium excretion, high urine output, and an increase in ADH (secondary and hence appropriate). Urine biochemical analysis will demonstrate dilute or concentrated urine and should be reviewed with simultaneous plasma osmolality assessment. ADH and ANP levels are high in both SIADH and CSWS, either as a primary or as a secondary event.

Biochemical criteria, however, may fail to distinguish between the two pathologies, and the key difference is the presence of volume depletion in CSWS.[3,22] Particular attention should be paid to skin turgor and mucous membranes. Intravascular volume can be assessed by examining jugular venous distension and by observation of orthostatic variations in blood pressure and pulse. Daily weight may provide helpful additional information because water accounts for a large proportion of body mass. Extracellular volume status can be difficult to assess clinically and may rarely be a confounding factor. In addition, some studies assessing volume status have highlighted the presence of hypovolemia in certain patients fulfilling the diagnostic criteria for SIADH.[33] This is due to the volume depletion of CSWS causing a secondary rise in ADH. Under such conditions, patients should correctly be diagnosed with CSWS rather than SIADH.[33]

The pathophysiologic changes and biochemical findings of SIADH and CSWS are summarized in Table 4 and a practical algorithm and differential for assessment of the hyponatremic patient are shown in Fig. 1 and Table 2.

Treatment of Hyponatremia

An expectant and supportive management strategy is best adopted in asymptomatic patients as the physiologic disturbance is often transient. Treatment is, however, indicated in the presence of acute symptomatic hyponatremia, which can be a prelude to life-threatening complications (see Table 1).

The correction of hyponatremia, especially in the chronic setting, can lead to neurologic sequelae.[9] This risk can be minimized by gradual correction of sodium deficits (see below). It is especially important to note that treatment should be targeted to the point of alleviation of symptoms rather than to the achievement of biochemical normality.[34]

Use of volume status to guide therapy in hyponatremia has produced varied results. Measurement of central venous pressure (CVP) and daily weight has been described to manage hyponatremic patients following SAH,[35] but this strategy is

TABLE 3. Diagnostic Criteria for SIADH

- Serum sodium <135 mmol/L
- Serum osmolality <280 mmol/kg
- Urine sodium >18 mmol/L
- Urine osmolality > serum osmolality
- Normal thyroid, adrenal, renal function
- Absence of peripheral edema or dehydration

TABLE 4. Biochemical and Water Changes in SIADH, CSWS, and Diabetes Insipidus (DI)

Finding	SIADH	CSWS	DI
Plasma volume	Raised	Lowered	Lowered
Sodium balance	Positive/equal	Negative	Equal
Water balance	Positive	Negative	Negative
Serum sodium	Low	Low	High
Serum osmolality	Lowered	High/normal	High
Urine sodium	High	High	Normal
Urine osmolality	High	Normal/high	Low

Normal values: plasma osmolality 278–305 mmol/kg, plasma sodium 135–145 mmol/L, urine osmolality 350–1000 mmol/kg, urine sodium 20–60 mmol/L, 100–250 mmol/24 h.

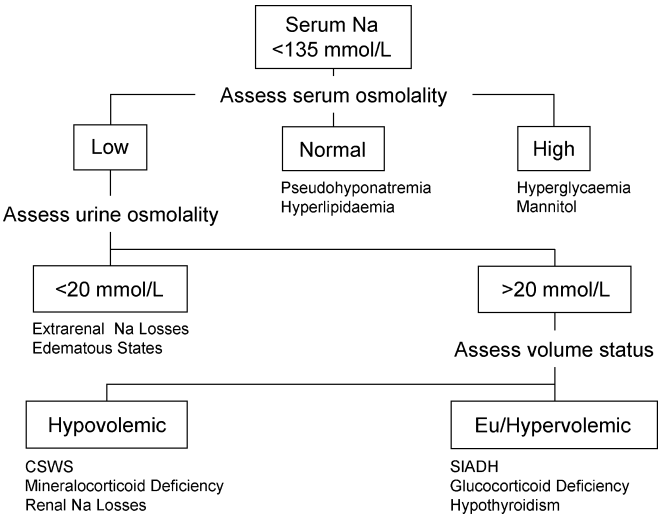

FIGURE 1. Algorithm for assessment of the hyponatremic patient.

prone to errors and the simple response to saline infusion may be more reliable.[36] CVP readings alone have been used to classify neurosurgical patients with hyponatremia and natriuresis as hypovolemic, normovolemic, or hypervolemic to guide therapy.[37] Hypovolemic patients received salt and additional amounts of fluid, while normovolemic patients received salt with standard maintenance fluid volumes. Seventy-five percent of patients achieved normal serum sodium within 72 hours with the nonresponding group requiring more aggressive therapy. The effect of intravenous fluid administration on serum sodium level can be estimated using simple formulas (Table 5).

Specific Treatment of SIADH

The appropriate management of SIADH is fluid restriction, initially to 1 L/day. This usually results in a slow rise in sodium of 1.5 mmol/L/day.[7] If supplemental intravenous fluid is required, 0.9% saline is the usual choice. More recent studies support this management strategy, although some authors recommend maintenance fluid replacement therapy with intravenous 5% dextrose.[38,39]

Pharmacologic treatment is a further option when the diagnosis is certain. SIADH treatment using furosemide is described,[40] with saline or salt supplementation to counteract the sodium loss that accompanies the free water loss. Lithium may be beneficial in patients with SIADH after brain trauma with dosage adjusted to maintain a plasma lithium concentration of 1 mmol/L.[41] Lithium acts as a blocker of 3,5-adenosine monophosphatase and inhibits the action of ADH on the renal tubule. The predictability and safety of this treatment have been questioned.[7] Demeclocycline is an ADH antagonist that can also be used in the treatment of SIADH. Initially democlocycline hydrochloride 900–1200 mg daily is given orally in divided doses, reduced after therapeutic effect is achieved to a daily oral maintenance dose of 600–900 mg. It is less toxic than lithium[42] but may take up to 3 weeks to achieve maximum effect.[9]

However, it should be remembered that many patients have self-limiting disease. In one study, one-third of consecutive neurosurgical patients fulfilled criteria for SIADH, but only half of these required treatment with fluid restriction, with the remainder achieving spontaneous resolution of their dysnatremias.[43]

TABLE 5. Formulas for Estimation of Effect of Intravenous Fluid Administration on Serum Sodium[64]

Δ serum $[Na^+]$ = infusate volume [(infusate $[Na^+]$ + infusate $[K^+]$) − serum $[Na^+]$ /(total body water + 1)

required Na^+ load = total body water (desired $[Na^+]$ − current $[Na^+]$)

Total body water can be estimated as a fraction of body weight.[65]

Specific Treatment of CSWS

Best management of CSWS is treatment with fluid and sodium resuscitation, although the saline solution used in the treatment of CSWS is more controversial. A 0.9% saline solution should generally be used in the first instance,[3] although in acute symptomatic hyponatremia, hypertonic (3%) saline has also been recommended,[7] with the administration of furosemide in the event of hypervolemia. Administration of 3% saline requires central venous access, and the use of 1.5% saline, which can be administered peripherally, has been advocated as an equally effective alternative.[3] It should be noted that administration of sodium in CSWS may, in some patients, drive further urinary sodium loss with accompanying loss of water. In cases refractory to salt and fluid therapy, prophylactic fludrocortisone may limit the negative sodium balance after SAH[44] by increasing sodium reabsorption from the renal tubule. Oral fludrocortisone doses of between 0.1 and 0.4 mg daily are recommended.[44,45] Care must be taken to ensure that hypokalemia does not then occur as a secondary effect.[46]

Neurologic Complications of Treatment of Hyponatremia

The dangers of rapid correction of hyponatremia are serious and well described[7,47] and remind us that the best treatments of sodium disturbance are often supportive with management of the underlying condition. Myelinolysis is a neurologic disorder affecting pontine and extrapontine structures that can occur after rapid elevation of serum sodium levels. Risk factors for its development include alcoholism, malnutrition, and liver disease. The symptoms and signs include mutism, dysarthria, and lethargy followed by spastic quadriparesis and pseudobulbar palsy. The risk of myelinolysis can be minimized by gradual correction of sodium deficit at a rate of less than 10 mmol/L/24 h, although lower correction rates are also reported.[47] Close monitoring of the hyponatremic patient undergoing treatment is mandatory; if overrapid correction is suspected, reversal using desmopressin and water may be appropriate.[48]

HYPERNATREMIA

Epidemiology

Hypernatremia is defined as serum sodium >145 mmol/L. It is less common than hyponatremia with an incidence of

around 1% across the spectrum of all hospital patients.[49,50] Hypernatremia is relatively more common in neurologic and critically ill patients than in the general in-patient population, and water depletion is especially common in the intensive care setting, where a 9% incidence of Na > 150 mmol/L has been reported.[51] Hypernatremia is often a paraphenomenon, being an indicator of the severity of the underlying disease process.

Causes

Hypernatremia is usually related to water deficiency, such as inadequate water supplementation or water loss, for example, associated with fever,[51] and only rarely does it represent salt excess, such as ingestion of salt or infusion of saline or hypertonic fluids.[52,53] Except in cases of uncontrollable diabetes insipidus, a hypernatremic state can only be maintained when access to water or thirst is impaired, and patients with altered mental state or decreased level of consciousness are therefore particularly susceptible.[54] The elderly are also at high risk, possibly owing to impaired urinary concentrating power, reduced thirst reflexes, and frailty resulting in the inability to access water.

Causes of hypernatremia are listed in Table 6 and include central and nephrogenic diabetes insipidus, dehydration, fever, and osmotic diuresis. Accounts of nephrogenic diabetes can be found elsewhere,[55,56] and this review will focus on central diabetes insipidus (CDI).

Central Diabetic Insipidus

CDI is a failure of homeostatic release of ADH from the hypothalamopituitary axis. It is characterized by the inability to concentrate urine and the passage of a large volume of inappropriately dilute urine with a consequent rise is plasma osmolality due to disproportionate loss of water over sodium and progressive dehydration. In neurologic practice, it is particularly associated with pituitary surgery,[57] TBI,[58] and anterior communicating artery aneurysmal SAH.[59] Patients who become brain dead often develop severe CDI, and this is particularly relevant in the management of potential organ donors.[60]

The anatomic and pathologic relationships of CDI have been reviewed previously.[61] Compromise of the hypothalamic centers or the supraoptic tract above the median eminence may lead to permanent CDI, whereas damage below the median eminence or removal of the posterior lobe of the pituitary leads to transient CDI because ADH is subsequently released from fibers ending in the median eminence.

The incidence of CDI in a neurosurgical unit has been reported as 3.7%,[59] with one-third following SAH, one-third following TBI, one-sixth after pituitary surgery, and one-sixth following intracerebral hemorrhage. Overall mortality in this group was high (72.4%), although this may be due in part to the fact that the bulk of the patients had experienced severe acute brain injury. The incidence of CDI after severe TBI is around 3% and is strongly associated with basal skull fracture.[39] Development of CDI in nonpituitary surgery patients is often associated with severe cerebral edema and impending death.[59] Pituitary stalk hematoma is a rare complicating factor after severe brain injury, and magnetic resonance imaging has been recommended for patients in whom the CDI is out of proportion to the severity of the injury.[62]

TABLE 6. Common Causes of Hypernatremia

Decreased ECF Volume
• Poor thirst/reduced water intake
• Intrarenal water loss
Diabetes insipidus
Central
Nephrogenic
Osmotic diuresis
Diuretics
• Extrarenal water loss
From respiratory tract
From gastrointestinal tract
Fever
Increased ECF Volume
• Iatrogenic: administration of sodium-containing fluids
• Mineralocorticoid excess
Primary hyperaldosteronism
Cushing syndrome
Exogenous

Investigation of the Hypernatremic Neurologic Patient

Clinical assessment of volume status allows differentiation between hypernatremic hypovolemia, with disproportionate water loss over sodium, and hypernatremic eu- or hypervolemia, resulting from hypertonic sodium gain. The majority of hypernatremic neurologic patients will be hypovolemic, and in this context, CDI must be distinguished from simple dehydration by urine volume assessment and biochemical analysis. Although conscious patients will become thirsty, neurologic patients may be cognitively impaired, either as a result of their primary pathology or the subsequent electrolyte disturbance, so thirst is often is an unreliable sign.

In the context of neurologic insult, the diagnosis of CDI can be made in the light of an abnormally high serum osmolality (>305 mmol/kg) and serum sodium (>145 mmol/L), in combination with an abnormally low urine osmolality (<350 mmol/kg), reflecting the inability of the kidney to concentrate urine in an appropriate manner. These laboratory tests may take some time and measurement of urine specific gravity (SG) is a useful adjunct to diagnosis when urgent treatment is required to prevent significant hypovolemia because of excessive urine volumes. A urine SG of less than 1.005, in the light of raised serum sodium, points strongly to a diagnosis of CDI. It is important to realize, however, that this criterion may provide a false negative when the serum sodium is grossly raised, and the diagnosis should therefore always be confirmed with laboratory measurement of urine and serum osmolality.

Neurologic patients may have other causes of water diuresis, including prehospital and intraoperative volume resuscitation. Diuresis of solute may also be caused by osmotic diuresis secondary to the use of mannitol or hypertonic saline, for control of intracranial pressure, or hyperglycemia. An

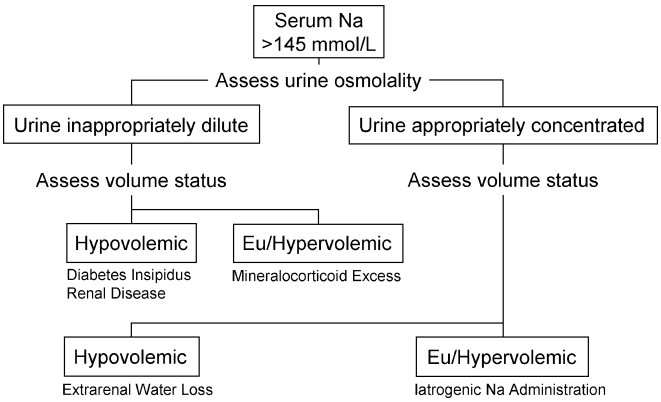

FIGURE 2. Algorithm for assessment of the hypernatremic patient.

algorithm for assessment of the hypernatremic patient is shown in Fig. 2.

Management of Hypernatremia

The management of the hypernatremic patient is invariably water replacement and retention. Rarely are patients hypernatremic as a result of excessive sodium administration, but such patients will respond to a normalization of intake. Conscious patients with CDI are able to increase oral intake, and if this fails or if urine output is greater than 250 mL/h, parenteral or intranasal vasopressin may be administered. Small doses, such as 1-deamino-8-D-arginine vasopressin (DDAVP) 0.4 μg intravenously or 100–200 μg intranasally, minimize the risk of an overprolonged action and can be repeated as required, dependent on clinical effect. In the unconscious patient, fluid replacement is best achieved with either intravenous 5% dextrose or water via a nasogastric tube with concomitant DDAVP administration. However, excessive intravenous fluid administration, given to replace high urinary output, may exacerbate the problem, and accurate clinical assessment of volume status is required to guide treatment. Saline solutions may aggravate the renal water loss because urine concentration cannot be achieved in the absence of ADH. Overrapid correction of hypernatremia may have serious consequences, most notably pulmonary and cerebral edema.[59] A reduction in serum sodium concentration of 10 mmol/L/day has therefore been suggested, with a more rapid reduction only indicated in those who have developed hypernatremia over of a period of hours.[54]

SUMMARY

Disturbances of sodium balance are common in the general in-patient hospital population but are more common in neurologic patients. A high index of suspicion should therefore be maintained in this patient group. In particular, the hyponatremic neurosurgical patient is at risk not only from the dysnatremia but also from the consequences of overtreatment. Asymptomatic patients can be managed successfully with a logical approach to diagnosis and a period of close monitoring. Treatment should be restricted to acute symptomatic patients in whom the associated mortality is significantly higher than the normal population.[63]

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