Hyponatremia and Hypernatremia: Disorders of Water Balance

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Abstract
Total body water and tonicity is tightly regulated by renal action of antidiuretic hormone (ADH), renin-angiotensin-aldosterone system, norepinephrine and by the thirst mechanism. Abnormalities in water balance are manifested as sodium disturbances—hyponatremia and hypernatremia. Hyponatremia ([Na⁺<136meq/l]) is a common abnormality in hospitalized patients and is associated with increased morbidity and mortality. A common cause of hyponatremia is impaired renal water excretion either due to low extracellular fluid volume or inappropriate secretion of ADH. Clinical assessment of total body water and urine studies help in determining cause and guiding treatment of hyponatremia. Acute and severe hyponatremia cause neurological symptoms necessitating rapid correction with hypertonic saline. Careful administration and monitoring of serum [Na⁺] is required to avoid overcorrection and complication of osmotic demyelination. Vasopressin receptor antagonists are being evaluated in management of euvoletic and hypervolemic hyponatremia. Hypernatremia ([Na⁺]>145meq/l) is caused by primary water deficit (with or without Na⁺ loss) and commonly occurs from inadequate access to water or impaired thirst mechanism. Assessment of the clinical circumstances and urine studies help determine the etiology, while management of hypernatremia involves fluid resuscitation and avoiding neurological complications from hyponatremia or its correction. Frequent monitoring of [Na⁺] is of paramount importance in the treatment of sodium disorders that overcomes the limitations of prediction equations. ©

INTRODUCTION

Disorders of serum sodium is a common electrolyte abnormality encountered in hospitalized patients. It is important for physicians to understand the pathophysiological mechanisms that cause hyponatremia and hypernatremia. The challenge in management lies in identifying the cause for the disorder of sodium and water balance. Instituting therapy needs to be carefully monitored as rapid correction can cause neurological sequelae. In this paper, we begin with a review of the physiology of water balance including the important role of vasopressin (antidiuretic hormone, ADH). We then discuss the pathophysiology, diagnosis and management of hyponatremia and hypernatremia and include a section on recent developments.

WATER HOMEOSTASIS

Serum tonicity refers to the forces that drive movement of water from one fluid compartment to another through a semi-permeable membrane. Serum osmolality (moles of solute/kgH₂O) is calculated as 2(Na⁺)+[(glucose/18)+((blood urea nitrogen/2.8)] with normal range=280-295mOsm/kgH₂O. Solutes such as Na⁺ and glucose that contribute to serum tonicity are termed effective osmoles, while urea and ethanol easily pass through cell membranes, thus contributing to serum osmolality but not tonicity.

Serum tonicity and sodium concentration are tightly regulated by equilibrium between water intake and water excretion. Mechanisms of osmoregulation and volume regulation play an important role in maintaining body water balance and tonicity (Fig. 1). Thirst is stimulated by the osmoreceptors in the hypothalamus (supra-optic nuclei) in response to increase in serum tonicity (2-3% increase or ≥290mOsm/kgH₂O). In addition, hypovolemia (≥10% loss in extracellular fluid-ECF) as sensed by the baroreceptors, induces thirst directly and by the renin-angiotensin system.¹

ADH is secreted by the posterior pituitary when stimulated by neurons from supra-optic and paraventricular nuclei of the hypothalamus. It acts on V2 receptors in the principal cells of the collecting tubules and inserts aquaporins on the apical surface that mediate water movement from the tubules to the hypertonic interstitium. The release of ADH is stimulated in response to hypertonicity and decreased ECF volume. Change in serum tonicity by as little as 1%
Hyponatremia is defined as serum $[Na^+] < 136 \text{meq/l}$. Hyponatremia is a common finding in hospitalized patients with a prevalence ranging from 15-30%. It is important to recognize hyponatremia as its presence is associated with increased mortality of 9-27% depending on the definition of hyponatremia.

Hyponatremia can be associated with low, normal or high tonicity. Hypotonic hyponatremia is the most common form of hyponatremia and is discussed below. Isotonic hyponatremia occurs with expansion of extracellular fluid with isotonic fluids that do not contain Na+ (for example-isotonic mannitol used for irrigation after transurethral prostatectomy and endometrial ablation) and thus there is no transcellular shift of water but the $[Na^+]$ decreases. Hypertonic hyponatremia is seen when there is increase in effective osmoles in the extracellular fluid (for example-hyperglycemia in insulin resistant states, hypertonic mannitol) with shift of water from the cells to the ECF and thus causing translocational hyponatremia. Of note, hyponatremia, as previously measured by the flame photometry method, was erroneously observed in patients with elevated triglycerides or proteins (from multiple myeloma) due to displacement of water (and Na+) from plasma. This laboratory artifact termed pseudohyponatremia has been overcome with the use of Na+ specific electrode as $[Na^+]$ measured in the aqueous phase of plasma by this method remains unaffected in hypertriglyceridemia or hyperproteinemia.

Hypotonic hyponatremia

Hypotonic hyponatremia occurs by two mechanisms (1) usual (or greater than usual) water intake in the setting of impaired renal water excretion leading to dilution of body solutes or less commonly (2) water intake in excess of the normal renal ability to excrete water. Hypotonic hyponatremia can be classified as hypovolemic, euvolemic and hypervolemic on the basis of ECF volume as assessed clinically (orthostatic changes in blood pressure and heart rate, edema, jugular venous distension, skin turgor, mucous membranes, ascites).

Pathophysiology of hyponatremia

Renal water excretion depends on the diluting ability of the nephron. Dilution of urine occurs with reabsorption of solutes by the Na-K-2Cl transporter in the thick ascending limb of loop of Henle, NaCl transporter in the distal convoluted tubule and the absence of ADH action at the collecting tubule. Dysfunction in these steps limits the ability to dilute urine and the maximum amount of urine that can be excreted. For example, if urine cannot be diluted below 350mOsm/ kgH2O, the maximum amount of water that can be excreted is 700/350=2 liters (as opposed to 700/50=14 liters of urine that can be excreted with maximum dilution to 50mOsm/ kgH2O). Water intake in excess of this renal (and extrarenal) water loss causes hyponatremia.

Causes of hypovolemic hyponatremia

Hyponatremia with decreased ECF volume occurs due to renal or extrarenal sodium and water loss. Diuretics are

alters the ADH release from the supra-optic nuclei. Maximal antidiuresis is achieved at tonicity ≥ 290mOsm/ kgH2O, while ADH is undetectable at tonicity <280mOsm/kgH2O. A ≥ 10% fall in ECF volume stimulates the baroreceptors that in turn increase ADH release from the paraventricular nuclei. Nausea, pain and pregnancy are other factors that alter ADH secretion. Numerous drugs affect sodium and water homeostasis, potentiate renal action of ADH or reset the osmostat threshold for release of ADH. Between these two mediators of ADH action, low circulating volume overrides the ADH suppression by hypotonicity. Thus, when required, the body sacrifices tonicity for maintenance of the ECF volume.

Regulation of body water balance depends on the ability of the kidney to excrete urine with an osmolality ranging from 50mOsm/kgH2O to a maximum of 1200mOsm/kgH2O. The volume of urine thus produced is necessary to excrete the dietary solute load (~700mOsm in western diet). Disturbance in body tonicity occurs due to disproportion between water and the effective osmoles and is manifested as hypernatremia or hyponatremia. Thus hypernatremia reflects a state where water content is relatively small for the sodium content and hyponatremia denotes water content being relatively large for the sodium content. Either disorder can occur in the setting of decreased, normal or increased sodium content. Thus, hypernatremia and hyponatremia should be considered disturbances in water rather than sodium balance.

**HYPONATREMIA**

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an important cause of renal water loss. Thiazide diuretics and loop diuretics impair the diluting ability by inhibiting the solute reabsorption in the diluting segment of the nephron. In addition, the resulting volume depletion causes ADH to be released. Most patients however do not develop hyponatremia as a large volume of urine can still be excreted. Thiazide diuretics are more likely than loop diuretics to cause hyponatremia as their action in the distal convoluted tubule in the cortex do not affect concentrating ability of the medullary interstitium. Thus, the urine osmolality may be 600mOsm/ kgH₂O in patients treated with hydrochlorothiazide. In contrast, loop diuretics inhibit the solute reabsorption in the ascending loop of Henle located in the outer medulla, thus also reducing the solute concentration in the medulla and its concentrating ability. Patients treated with furosemide thus may maximally dilute the urine to 300mOsm/kgH₂O. Osmotic diuresis and hemorrhage. Release of brain natriuretic peptide in cerebral dysfunction is a probable mechanism causing renal sodium and water losses leading to hypovolemia and hyponatremia. Advanced chronic kidney disease (glomerular filtration rate GFR<15ml/min) is another cause for renal sodium loss (salt dilution. A similar mechanism also causes hyponatremia wasting nephropathy) due to tubular dysfunction and low tubular flow rates causing osmotic equilibration between the luminal fluid and medullary interstitium and thus impaired dilution. A similar mechanism also causes hyponatremia seen in the recovery phase of acute tubular necrosis and post-obstructive diuresis. Extrarenal water and sodium loss occurs in vomiting, diarrhea, hemorrhage, excessive sweating (marathon runners), and fluid sequestration in third space. Replacement of volume losses with electrolyte free water causes hyponatremia.

Cerebral salt wasting syndrome is a rare disorder seen in neurosurgical patients and those with subarachnoid hemorrhage. Release of brain natriuretic peptide in cerebral dysfunction is a probable mechanism causing renal sodium and water losses leading to hypovolemia and hyponatremia. Advanced chronic kidney disease (glomerular filtration rate GFR<15ml/min) is another cause for renal sodium loss (salt wasting nephropathy) due to tubular dysfunction and low tubular flow rates causing osmotic equilibration between the luminal fluid and medullary interstitium and thus impaired dilution. A similar mechanism also causes hyponatremia seen in the recovery phase of acute tubular necrosis and post-obstructive diuresis. Extrarenal water and sodium loss occurs in vomiting, diarrhea, hemorrhage, excessive sweating (marathon runners), and fluid sequestration in third space. Replacement of volume losses with electrolyte free water causes hyponatremia.

Hyponatremia with normal ECF volume is seen in syndrome of inappropriate antidiuresis (SIAD) and endocrine deficiency (hypothyroidism or adrenal insufficiency). SIAD may be a more accurate term than the earlier term ‘syndrome of inappropriate antidiuretic hormone (SIADH)’. ADH is inappropriately elevated (i.e. in the absence of hypovolemia) in SIAD by a variety of mechanisms (Table 1) including (1) enhanced and unregulated ADH secretion (by tumor or hypothalamus) (2) elevated secretion of ADH in basal state and in response to hypertonicity (3) reset osmostat (i.e. serum osmolality level lower than normal below which ADH secretion is suppressed) (4) activating mutation of the V2 receptor permitting reabsorption of water in absence of ADH. Despite water reabsorption by ADH, volume status remains stable or mildly increased due to escape mechanisms that regulate volume expansion including increased renal solute loss (due to pressure natriuresis and atrial natriuretic peptide) and water loss (downregulation of aquaporin-2). Clinical features of SIAD include plasma hypotonicity, clinical euvoolemia, urine osmolality >100mOsm/kgH₂O, urine >40meq/l while on normal sodium intake, normal GFR, absence of diuretic use, normal adrenal and thyroid function and failure to correct hyponatremia (<5meq/l rise in serum Na⁺) with 0.9% normal saline load (2 liters over 24-48hrs).

Hypothyroidism or adrenal insufficiency impairs water excretion by reduced cardiac output or stroke volume leading to ADH release. In addition, isolated glucocorticoid deficiency increases ADH secretion, possibly through corticotropin releasing factor mediated release of ADH. Correction of these hormonal deficits corrects for the water excretion defect and hyponatremia. Other causes for euvolemic hyponatremia include pain, nausea, or hypotonic fluid administration in the post-operative setting. Human immunodeficiency virus (HIV) infection may cause hyponatremia through SIAD (Pneumocystis

**Table 1 : Causes of syndrome of inappropriate antidiuresis:**

| Malignancy | Bronchogenic (small cell cancer) |
| Head and neck | Pancreas |
| Pulmonary disorders | Viral and bacterial pneumonia |
| Tuberculosis | Lung abscess |
| Empyema | Advanced chronic obstructive pulmonary disease |
| Ventilator dependent respiratory failure | Neurologic disorder |
| Meningo-encephalitis | Head trauma |
| Stroke | Brain tumor |
| Subdural hematoma | ADH analogues |
| Desmopressin | Oxytocin |
| Thioxanthenes | Haloperidol |
| Drugs that increase ADH release or potentiate ADH action | Chlorpropamide |
| Tricyclic antidepressants | Carbamazepine, oxcarbamazepine |
| Vincristine, vinblastine | Cyclophosphamide, ifosfamide |
| Bromocriptine | Selective serotonin reuptake inhibitors |
| Morphine, demerol, methadone | Phenothiazine |
| Non-steroidal anti-inflammatory drugs | Clofibrate |
| Other | HIV/AIDS |
| Acute psychosis | Acute intermittent porphyria |
| Idiopathic | Surgical or emotional stress |
| Nausea or emesis | ADH=antidiuretic hormone, HIV/AIDS=human immunodeficiency virus/ acquired immunodeficiency syndrome. |
carinii pneumonia, central nervous system infections or malignancies), adrenal insufficiency or gastrointestinal losses. Exercise induced hyponatremia is not uncommonly seen among long distance marathon runners especially in females and with low body weight. Excessive drinking of hypotonic solutions (>1.5l/hour of water or hypotonic sport drinks) and inappropriate secretion of ADH due to muscle derived interleukin-6 are probable mechanisms causing hyponatremia in runners. 

Primary polydipsia (compulsive drinking 10-15 liter/day) is seen among psychiatric patients especially with schizophrenia. Probable mechanisms of hyponatremia in these patients include central defect in thirst regulation, excessive secretion or renal action of ADH and antipsychotic drugs that by its anticholinergic action cause dry mouth thus enhancing thirst. A low dietary solute intake (tea-toast diet) as in debilitated residents in nursing homes or chronic alcohol ingestion (beer potomania) causes hyponatremia by decreasing the ability of the kidney to excrete water (for example- a 100mOsm solute diet would be excreted in a urine output of 100/50 = 2 liter at maximal dilution). Water intake above this renal and insensible water loss will cause hyponatremia. Urine osmolality in primary polydipsia and low solute intake is maximally dilute (<100mOsm/kgH2O).

Hyponatremia with increased ECF volume is seen in patients with congestive heart failure, nephrotic syndrome and hepatic cirrhosis. The common mechanism is low intravascular filling from low cardiac output (as in heart failure) or movement of water from the vascular to the interstitial space (due to hypoalbuminemia in nephrotic syndrome and cirrhosis). Activation of the neurohormonal compensatory mechanisms (renin-angiotensin-aldosterone, ADH and norepinephrine) causes water and salt retention leading to hyponatremia and hypervolemia.

Clinical diagnosis

Neurological symptoms from hyponatremia occur due to transcellular movement of water from the hypotonic ECF into the central nervous system. Swelling of the neurons is manifested as headache, lethargy, confusion, gait disorder, nausea, vomiting and in severe hyponatremia as seizures, coma, permanent brain damage or death. Severe hyponatremia (Na⁺<120meq/l) and rapid development of hyponatremia (<48 hours) are associated with development of neurological symptoms. A slower decline in Na⁺ is less likely to be symptomatic as the neurons adapt to this new state and restore cell volume by moving out solutes (Na⁺, K⁺) and organic osmolytes (glutamine, glutamate, taurine, inositol).

Laboratory diagnosis

Serum osmolality <280mOsm/kgH2O confirms hypotonicity as hyponatremia with hypertoncity (or isotoncity) require treatment directed at the underlying cause for electrolyte imbalance rather than directed at Hyponatremia (Fig. 2). Urine osmolality distinguishes patients with appropriately dilute urine (<100mOsm/kgH2O as in primary polydipsia or low-solute intake) from patients with impaired diluting ability as usually seen in hyponatremic patients like SIAD (urine osmolality >100mOsm/kgH2O). In some patients with reset osmostat, urine osmolality may be <100mOsm/kgH2O if fluid intake is great enough to lower serum osmolality below the new osmotic 'set point', thus suppressing ADH and causing maximal urine dilution. Urine [Na⁺] is elevated (>40meq/l) in patients with SIAD and renal salt wasting while it is low (<20meq/l) in patients with ECF volume depletion from extrarenal cause.

Acid-base disturbances may help identify the cause for hyponatremia when not clearly apparent. Metabolic alkalosis with hypokalemia is seen with diuretic use or vomiting, metabolic acidosis and hypokalemia suggests diarrhoea while metabolic acidosis and hyperkalemia occurs with adrenal insufficiency. Low uric acid level (<4mg/dl) is seen in patients with SIAD or hypervolemia due to increased uric acid excretion in the urine in contrast to patients with hypovolemia having higher level of uric acid.

Treatment

Treatment of hyponatremia depends on (1) the presence of neurological symptoms and (2) the cause for the hyponatremia. Symptomatic hyponatremia is a medical emergency. Patients presenting with seizures or other severe neurological symptoms suggestive of cerebral edema need a fast rate of correction (1.5-2meq/l/h for the first 3-4 hours; total 8-12meq/l/day) and this is achieved with administration of hypertonic saline (3% NaCl). Correction of hyponatremia is done till symptoms resolve. If symptoms do not resolve with this correction, the upper limit may have to be exceeded cautiously with consideration of the balance between risks of hyponatremia against the risk of correction in each patient individually.

![Fig. 2: Algorithm for diagnosis and management of hyponatremia.](image-url)
Patients who are asymptomatic from the chronic or slowly developing hyponatremia need a slower rate of correction averaging 0.5meq/l/h (total 8-12meq/l/day). Rapid correction of hyponatremia increases the risk for osmotic demyelination (central pontine myelinolysis). This may occur due to movement of water out of the edematous neurons, causing shrinkage and disruption of interaction with their myelin sheaths. Patients that are more prone for osmotic demyelination include women, patients with chronic alcohol abuse, hepatic failure and malnutrition. Central pontine myelinolysis (CPM) presents with fatal outcomes - quadriplegia, pseudobulbar palsy, seizures, coma and death. Thus, it is very important to keep this grave complication in mind while correcting hyponatremia. However, reversing the primary neurological injury in patients with symptomatic hyponatremia with rapid but careful correction outweighs the risk of CPM.

Equations are available to help calculate the initial rate of fluids to be administered. A widely used formula is the Adrogue-Madias formula:10

\[
\text{Change in serum Na}^+\text{ with infusing solution} = \left[ \text{infusate Na}^+ + \text{infusate K}^+ \right] - \text{serum Na}^+ \times \text{total body water} + 1
\]

Infusate Na\(^+\) is the [Na\(^+\)] in the infused fluid (154meq/l in 0.9%NS, 513meq/l in 3%NS, 77meq/l in 0.45%NS and 0meq/l in D5W). Total body water is calculated as total body weight X0.6 in children and nonelderly men, X0.5 in nonelderly women and elderly men and X0.45 in elderly women. The above equation predicts the amount of [Na\(^+\)] change by 1 liter of infusate. Dividing the targeted change in serum sodium by the result of the above equation gives the volume of infusate required and thus the rate of infusion. This equation assumes that there is no other source of fluid gain or losses and so is useful in guiding the initial rate of therapy. Na\(^+\) should be measured frequently during treatment (every 2-4 hours) and adjustments made in the infusion rate, tonicity of infusate and furosemide dose as necessary.

Fluid restriction (upto 800-1000ml/day) is useful in patients with euvoilemic and hypervolemic hyponatremia to induce negative water balance, but is difficult to follow. In patients with hypovolemia, isotonic saline corrects hyponatremia due to its salt content (osmolality of 0.9NS=308meq/l) and corrects the volume deficit thus removing the stimulus for ADH.

Adequate dose of furosemide helps limit ECF expansion in euvoilemic and hypervolemic hyponatremia by inducing excretion of 70-80meq/l urine Na\(^+\) and K\(^+\) (tonicity similar to 0.45NS). Replacement of these electrolyte losses with 0.9NS would require a volume equal to half the urine output, with the resulting net free water clearance being half the total urine volume. Demeclocycline impairs ADH action on the collecting duct (thus inducing reversible nephrogenic diabetes insipidus) and can be used for treatment of chronic asymptomatic hyponatremia due to SIAD if fluid retention alone does not restore Na\(^+\). It needs close monitoring for development of renal failure or hypersalinaemia especially in patients with fluid restriction. Hormonal deficiency (hypothyroidism and adrenal insufficiency) should be identified and corrected promptly. Patients with hyponatremia from primary polydipsia or reduced solute intake usually recover with water restriction.

Recent developments

The accuracy of Adrogue-Madias formula in predicting change in serum Na\(^+\) was evaluated in a retrospective study on patients administered hypertonic saline (3%NS) for correction of hyponatremia.12 Among 31 patients with pretreatment serum Na\(^+\)<120meq/l, the Adrogue-Madias formula underestimated the rise in serum Na\(^+\) i.e. the actual increase in serum Na\(^+\) was greater than that predicted by the formula. These findings are contrary to another study on patients receiving intravenous fluids (0.9 NS and 3% NS) for treatment of hyponatremia that showed the Adrogue-Madias formula to have a good predictive accuracy except in patients with ECF depletion and psychogenic polydipsia where it tended to underestimate the Na\(^+\) correction.13 Other formulas like the Barsoum-Levine and the Nguyen-Kurtz exist to guide hyponatremia management but have their own limitations.14 These findings stress the importance of mandatory and careful monitoring of [Na\(^+\)] and urine output during correction of hyponatremia.

Vasopressin receptor antagonists (vaptan) is a new class of drugs being studied in the management of euvoilemic and hypervolemic hyponatremia. These drugs are different from diuretics in that vaptans induce aquareisis (free water excretion) without affecting the clearance of electrolytes. Vaptans mobilize water from the extracellular and intracellular compartments unlike diuretics which cause activation of the renin-angiotensin system from intravascular volume depletion. V1a receptors, present in vascular smooth muscle, mediate vasoconstriction and myocardial hypertrophy. V2 receptors are the site of ADH action on the principal cells of the collecting duct. Clinical trials evaluating the effect of vaptans in heart failure (acute exacerbations, chronic state), SIAD and cirrhosis are discussed elsewhere.15 In general, the vaptans are well tolerated with demonstrated improvement in serum Na\(^+\), increased urine output, reduction in body weight and edema, symptomatic improvement of dyspnea and improved mental health. Some trials showed efficacy of vaptans in the absence of fluid restriction. No long term benefit on mortality or heart failure hospitalizations has been shown. Side effects include increased thirst, dry mouth and the risk of hypernatremia from overcorrection. Intravenous conivaptan (V1a/V2 receptor antagonist) is approved by US Food and Drug Administration for inpatient treatment of euvoilemic or hypervolemic hyponatremia. Vaptans are not suitable for hyponatremia due to hypovolemia, cerebral salt wasting and psychogenic polydipsia where the ADH level is appropriate. Thus, it is vital to identify the cause for hyponatremia before choosing vaptans in the treatment of hyponatremia and closely monitor for hypernatremia and acute renal failure due to excessive water excretion and
rapid correction of Na⁺.

**Hypernatremia**

Hypernatremia ([Na⁺]>145meq/l) occurs in patients with inadequate access to water or impaired thirst mechanism usually in infants or elderly adults. Hypernatremia is seen in about 1% of hospitalized patients and is more common (7%) in intensive care unit patients. Mortality rate as high as 40% is reported with hypernatremia, though it is uncommonly identified as the primary cause of death.

**Pathophysiology of hypernatremia**

Hypernatremia represents a state of relative excess of Na⁺ to water in the ECF. Causes for hypernatremia include primary water deficit (with or without Na⁺ loss) and Na⁺ gain (Table 2). Water deficit is the most common cause of hypernatremia that develops either from inadequate intake or increased loss of free water. Advanced age, dementia, mental status changes can lead to inadequate access to water. Adipsic hypernatremia (sometimes called essential hypernatremia) results from congenital or acquired defect in hypothalamic osmoreceptors. It is associated with partial or complete loss of osmoregulation of vasopressin, lack of thirst, hypernatremia and evidence of hypovolemia. Patients with this condition may have associated elevated renin and aldosterone, hypokalemia and alkalosis.

Renal water loss can occur due to impaired ability of the kidneys to concentrate urine. Failure of vasopressin action either from reduced pituitary secretion (central diabetes insipidus DI) or resistance at the level of collecting tubules (nephrogenic DI) prevents reabsorption of water thus causing hypernatremia. Patients with DI excrete large amount of inappropriately dilute urine as opposed to small amount of concentrated urine seen in patients with extrarenal fluid losses. 24 hour urine solute excretion is normal in DI as opposed to elevated solute excretion seen in osmotic diuresis. Patients with DI generally do not develop hypernatremia if they are able to maintain fluid intake adequate to compensate for the water loss. Loop diuretics, osmotic diuresis (from hyperglycemia, mannitol, increased urea excretion from high protein diet) and renal disease can also lead to increased renal fluid losses.

Extrarenal fluid losses can result from the skin (e.g., burns, fever and exercise), gastrointestinal tract (e.g., vomiting, viral gastroenteritis, and osmotic diarrhea) and respiratory tract (e.g., mechanical ventilation). Secretory diarrhea patients e.g., VIPoma, carcinoid syndrome, and cholera, generally do not present with hypernatremia due to loss of both electrolytes and water. Transient hypernatremia can develop after seizures or vigorous exercise due to the shift of water into ICF compartment.

**Sodium excess**

Sodium excess with use of parenteral electrolyte solutions is an iatrogenic cause of hypernatremia in the hospital setting (for example- replacement of insensible losses with 0.9% normal saline). It can also be seen after use of sodium bicarbonate for correction of metabolic acidosis or in cardiopulmonary resuscitation. Use of high sodium dialysate in dialysis, intrauterine instillation of hypertonic saline for the termination of pregnancy, problems with breastfeeding or use of improperly prepared infant formula in infants, ingestion of sea water, salt or baking soda are also associated with hypernatremia. Inappropriate salt reabsorption in hyperaldosteronism is also associated with hypernatremia which is generally mild and asymptomatic.

**Clinical diagnosis**

Patients with hypernatremia present with non specific neurological symptoms including lethargy, coma, neuromuscular irritability, and seizures although seizures are more common during therapy. Hypernatremic dehydration can cause venous sinus thrombosis. Hypernatremia causes transcellular movement of water out of the neurons and shrinkage of brain which can result in further complication of intracranial hemorrhage by tearing of blood vessels. Alternatively rapid correction of hypernatremia can result in brain swelling due to the lack of sufficient time for the removal of osmolytes produced by brain which can cause permanent brain damage. Patients present with thirst and signs of water deficit (e.g., hypovolemia, postural hypotension and tachycardia). Other symptoms might point to an etiological factor like polyuria, diarrhea, fever etc.

**Laboratory diagnosis**

An assessment of clinical circumstances, acuity and volume status is of paramount importance in the

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**Table 2: Causes of hypernatremia**

<table>
<thead>
<tr>
<th>Type of Deficit</th>
<th>Causes</th>
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<tr>
<td>Pure Water deficit</td>
<td>- Inadequate intake (e.g., Poor water access due to debility, Adipsic hypernatremia) - Insensible losses (Skin, Respiratory tract (mechanical ventilation)) - Renal Loss (Diabetes insipidus (Primary Central or Nephrogenic DI, Secondary Central or Nephrogenic DI e.g., head trauma, neoplasm, renal disease, hypercalcemia, hypokalemia, pregnancy, Lithium, Demeocalecine, Methoxyflurane, Foscarnet, Aminoiglycosides, Amphotericin B, Cidofovir, Vaptans) - Water and Sodium deficit (Extrarenal Loss (Skin (burns, excessive sweating) Gastrointestinal Tract (viral gastroenteritis, osmotic diarrhea e.g. lactulose, vomiting,) - Renal Loss (Loop Diuretics, Osmotic diuresis (Hyperglycemia, Mannitol, High Protein Diet, Tissue catabolism), Renal disease, Post obstructive diuresis, Resolving or polyuric ATN) - Sodium Gain (iatrogenic, hyperaldosteronism, Cushing’s syndrome, Sea water intake, Ingestion of salt or baking soda, Hypertonic feeding) - Transient (After seizures or vigorous exercise)</td>
</tr>
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management of hypernatremia (Fig. 3). Patients with hypotonic fluid loss can be more hypovolemic if potassium is also lost concurrently. Pure water loss is associated with a lesser degree of ECF volume contraction than hypotonic fluid loss as most of the lost water comes from ICF compartment. As a result hypovolemia may not be evident clinically in patients who have lost pure water e.g., DI, and insensible losses. Serum glucose should be checked in all patients to rule out osmotic diuresis. Measurement of urine output and urine osmolality helps in the determination of etiology. Measurement of urine Na⁺ can help in the assessment of the volume status of the patient. Diuretic use can confuse the picture by altering urine sodium. A low urine Na⁺ (<10 meq/L) with urine osmolality greater than 800 mOsm/kgH₂O is seen in hypovolemic patients with extrarenal and remote renal fluid losses or inadequate water intake. An elevation of urine osmolality with urine sodium greater than 100 meq/L can be seen in patients who have received hypertonic fluids and thus have developed hypervolemia. Polyuric patients with osmotic diuresis present with urine osmolality greater than 300 mosmol/kg and elevated total solute excretion. Daily solute load on a typical western diet is approximately 600-900 mosmol/day which is mostly excreted as electrolytes and urea. A 24 hour urine solute output greater than 900 mosmol/day suggests osmotic diuresis or the use of diuretics. Urine glucose and urea nitrogen should be measured if osmotic diuresis is suspected.

In DI, total daily solute excretion is normal. Water deprivation test can differentiate between different types of DI. In complete central and nephrogenic DI, urine osmolality is generally less than 300 mosmol/kg. It can be differentiated further. More than 50% rise in urine osmolality by desmopressin administration indicates complete central DI, whereas a lack of response indicates complete nephrogenic DI. In partial diabetes insipidus, urine osmolality can be between 300 and 800 mosmol/kg in response to a water deprivation test. A distinction between partial central and partial nephrogenic DI can be made during water deprivation test by the concurrent measurements of plasma osmolality, urine osmolality and vasopressin level. It may require the administration of hypertonic saline.

Serum creatinine, potassium, calcium, osmolality, and blood urea nitrogen should also be checked in all patients. Further laboratory and radiological tests may be needed for specific etiologies especially if an abnormality in hypothalamo-neurohypophyseal region is suspected.

Treatment

Multiple formulas have been proposed for the management of hypernatremia. The following is the traditionally used formula for the calculation of water deficit.

Water deficit = Total Body Water X ([Serum Na⁺ / 140] – 1)

As this formula can underestimate the amount of water deficit in patients with hypotonic fluid loss rather than pure water loss, Adrogué et al have suggested an alternate formula predicting the effect of 1000ml of an infusate as follows:18

Change in serum Na⁺ = (([infusate Na⁺ + infusate K⁺]-serum Na⁺) / (Total Body Water + 1 Liter))

[Na⁺] in the infused fluid and total body water is calculated as previously described under hyponatremia. This formula gives flexibility in selection of the infusing fluid and means to predict the sodium correction rate. It is limited as it does not account for ongoing losses (including insensible losses) which must be taken into account during Na⁺ correction as continued losses makes the correction slower. This probably led to its failure in prediction of Na⁺ correction in a subset of patients with severe extracellular volume depletion and marked reduction of renal function in the study by Liamis et al.13 Other electrolytes like K⁺, Mg²⁺, Ca²⁺ and phosphorus should also be monitored serially. Ongoing fluid losses including insensible fluid losses must be taken into account.

If the development of hypernatremia has been acute (in hours) usually from sodium gain, Na⁺ can be corrected at a rate of 1 meq/l/hour. If hypernatremia has developed more slowly (days), a correction rate of 0.5 meq/L/Hour is
more appropriate. Na+ should not be corrected by >10-12 meq/l over the first 24 hours to prevent the development of cerebral edema and permanent brain damage. The goal of correction should be to bring Na+ to 145 meq/L. Water deficit should be corrected over a period of 48 to 72 hours.

Enteral free water intake is the safest way to correct hypernatremia. It may require the placement of a nasogastric tube if the patient is unable to drink fluids. Parenteral hypotonic fluids like D5W, 0.22% (quarter-normal) saline or 0.45% (half-normal) saline can also be administered. Pure free water (as in D5W) is preferred in cases of relative pure free water losses like DI and insensible losses. Insulin might be needed with D5W if hyperglycemia is present to prevent osmotic diuresis. Cerebral edema might occur if blood glucose is lowered too rapidly with insulin. In other cases, 0.22% (quarter-normal) saline or 0.45% (half-normal) saline may be used. 0.9% normal saline may be used for the initial stabilization of patients with hemodynamic compromise. 3% (hypertonic) saline may have to be given if patient develops neurological symptoms from rapid correction. In patients with sodium excess, a combination of furosemide with free water like D5W can be tried. Furosemide alone should not be given as it will then exacerbate hypernatremia by causing the excretion of hypotonic urine. Patients may need dialysis if severe renal failure is present.

In central DI, desmopressin is very helpful and is available as pills and nasal spray. If the central DI is only partial, other medications that aid in vasopressin secretion or action may help e.g. chlorpropamide, carbamazepine, and clofibrate. Thiazides demonstrate paradoxical antidiuretic effect in DI by increasing proximal tubular water and sodium reabsorption. Nephrogenic DI is commonly acquired from underlying causes like hypercalcemia and hypokalemia and they should be treated. Offending drugs e.g. lithium should be discontinued if possible. Thiazides with or without amiloride and non-steroidal anti-inflammatory drugs e.g., indomethacin, have been demonstrated to be useful. Amiloride reduces the uptake of lithium in the principal cells of collecting duct and is considered useful in lithium induced nephrogenic diabetes insipidus. A decreased solute load with a low salt and low protein diet also helps.

In patients with adipsia/hypodipsia, Na+ correction should be followed by daily measurement of weight and estimation of volume status. Acute presentations of adipsic hypernatremia are treated by rehydration with free water or hypotonic fluids. Patients with partial loss of osmoregulation of vasopressin, develop a reduction in vasopressin level and subsequent polyuria before hypernatremia is fully corrected. They may appear clinically to be having a reset osmostat and may need desmopressin or chlorpropamide in addition to fluids. Patients with complete loss of osmoregulation of vasopressin have a relatively fixed vasopressin secretion rate and can go into hypernatremia or hypotonicemia if they drink too less or too much respectively.

Recent developments

A recently published study evaluated multiple proposed formulas for the guidance of treatment including those recommended by Adrogué-Madias, Barsoum-Levine and Kurtz-Nguyen. Although good correlation was noticed for the group as a whole, no formula was able to predict sodium correction accurately in an individual patient. Individual variations were too high. The results from this study have thus again underscored the importance of serial monitoring of serum sodium and the periodic adjustment of therapy accordingly.

**CONCLUSION**

Hyponatremia and hypernatremia represent disorders of water balance. Impaired renal water excretion and ADH play an important role in hypernatremia, while excess water loss leads to hypernatremia. Both hyponatremia and hypernatremia present with non-specific neurological symptoms and the physician must recognize these electrolyte imbalances as a cause for reversible encephalopathy. Meticulous clinical history and physical examination with the help of laboratory studies point to the cause for hypo- or hypernatremia and guide therapy. Careful correction of sodium level is warranted to avoid fatal neurological sequelae.

**REFERENCES**


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Announcement

18th All India Post Graduate Training Programme For Internal Medicine & Dip. N.B. Students conducted by API Chennai Chapter.

**Dates:** 19th, 20th & 21st December – 2008 (Friday to Sunday)

**Venue:** Panagal Hall, Kilpauk Medical College, Chennai – 600 010

**Registration:** Rs. 500/- (Rupees Five Hundred only) cash / D/D

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