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Hyponatremia: A practical approach

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Abstract

Hyponatremia is an important and common clinical problem. The etiology is multifactorial. Hyponatremia may be euvolemic, hypovolemic or hypervolemic. Proper interpretation of the various laboratory tests helps to differentiate the various types of hyponatremia. Treatment varies with the nature of onset -acute or chronic, severity and symptoms. Normal saline forms the mainstay of treatment for hypovolemic hyponatremia while 3% NaCl and fluid restriction are important for euvolemic hyponatremia. Hypervolemic hyponatremia responds well to fluid restriction and diuretics. There have been several recent advances in the last year with revision in the guidelines for treatment and availability of vaptans. Judicious use of vaptans may help in treatment of hyponatremia.

Keywords: Hyponatremia-Euvolemic, osmolality, osmotic demyelination, SIADH, Vaptans

Objectives

Hyponatremia is a commonly encountered problem. The varied etiologies of hyponatremia and the multiple formulae for its correction make it a nightmare for the students and physicians alike. The guidelines for management of hyponatremia have been revised recently and, in addition new agents (vaptans) have become available in market for treatment of hyponatremia. The objective of this article is to apprise the clinician with the latest protocols for management of hyponatremia and current guidelines for the use of vaptans.

Definition

Hyponatremia is defined as a serum sodium <135 meq/l.[1]

Epidemiology

Hyponatremia is seen in in 15-30% in hospital setting esp. in Intensive care units.[2]

Pathogenesis of hyponatremia

Hyponatremia results from the inability of the kidney to excrete a water load or excess water intake. Water intake depends upon thirst mechanism. Thirst is stimulated by increase in osmolality. Thirst is sensed by osmoreceptors located in the hypothalamus and leads to the release of anti-diuretic hormone (vasopressin) from the posterior pituitary. Antidiuretic hormone acts on the V2 receptors located at the basolateral aspect of the collecting duct cells and leads to increased aquaporin expression on the luminal aspect of the collecting duct cells which increases water absorption and abolishes thirst.

Hyponatremia occurs if there is persistent ADH stimulation which is seen in following situations.

- Normal but persistent ADH secretion-In volume depletion the effect of decreased volume counteracts the effect of hypoosmolality and ADH stimulation continues to occur. Effective arterial blood volume depletion occurs by two mechanisms: True volume depletion; and in edematous patients with heart failure or cirrhosis in whom tissue perfusion is reduced because of a low cardiac output or arterial vasodilation, respectively. The reduction in tissue perfusion is sensed by baroreceptors at three sites: (i) In the carotid sinus and aortic arch that regulate sympathetic activity and, with significant volume depletion, the release of antidiuretic hormone; (ii) In the glomerular afferent arterioles that regulate the activity of the renin-angiotensin system; and (iii) in the atria and ventricles that regulate the release of natriuretic peptides. As a result there is water retention
- Abnormal ADH secretion e.g. Syndrome of inappropriate ADH release described below (SIADH).

Symptoms

Acute hyponatremia is characterized by onset of symptoms <48h. Patients with acute hyponatremia develop neurologic symptoms resulting from cerebral edema induced by water movement into the brain. These may include seizures, impaired mental status or coma and death.

Chronic hyponatremia- Hyponatremia developing over >48 h should be considered “chronic.” Most patients have chronic hyponatremia. The serum sodium concentration is usually above 120meq/L. Brain adapts itself to hyponatremia by generation of idiogenic osmoles. This is a protective mechanism that reduces the degree of cerebral edema; it begins on the first day and is complete within several days. Hence in chronic hyponatremia patients may appear asymptomatic. Mild hyponatremia is characterized by gastrointestinal tract symptoms nausea, vomiting, loss of appetite. Sometimes, subtle neurologic abnormalities may be present when the serum sodium is between 120 and 130 meq/L. Hyponatremia in the elderly may manifest with frequent falls and gait disturbances.[3]

Classification of hyponatremia

Hyponatremia is classified as pseudo hyponatremia, true and translocational hyponatremia [Figure 1].

Normal serum osmolality is 280-295 mosm/kg. The serum osmolality (S Osm) can be calculated by the concentration in millimoles per liter of the major serum solutes according to the following equation: Sosm (mmol/kg) = (2 × serum [Na]) + (serum [glucose]/18) + (blood urea nitrogen/2.8).

Pseudo (normo-osmolal) or isotonic hyponatremia is due to presence of hypertriglyceridemia or increase in plasma proteins in conditions such as multiple myeloma. In normal subjects, the plasma water is 93 percent of the plasma volume, fats and proteins account for the remaining 7 percent. Plasma water fraction falls below 80 percent in cases with marked hyperlipidemia (triglycerides >1500 mg/dL) or hyperproteinemia (protein >10 g/dL).[4,5] Here, the plasma water sodium concentration and plasma osmolality are unchanged, but the measured sodium concentration in the total plasma volume is reduced

since the specimen contains less plasma water. In renal failure, the elevation in blood urea counteracts the fall in serum osmolality due to hyponatremia. However, the effective serum osmolality is appropriately reduced in this setting since urea is an ineffective osmole.

Translocational (hyperosmolal) or hypertonic or redistributive hyponatremia is due to presence of osmotically active solutes in the serum e.g., mannitol or glucose.[6] When the plasma contains significant amounts of unmeasured solutes, such as mannitol or radiographic contrast agents, plasma osmolality cannot be calculated accurately and must be ascertained by direct measurement.

True (hypoosmolal) hyponatremia is associated with reduction in serum osmolality and is further classified as euvolemic, hypervolemic and hypovolemic[7,8,9] [Figure 2].

Etiology of true hyponatremia

Hypovolemia hyponatremia

It is associated with low plasma volume. The causes of hypovolemic hyponatremia may be renal or non-renal [Figure 2].

Cerebral salt wasting (CSW): Resembles SIADH [Table 1] except that in CSW renal salt wasting and volume depletion is the main defect with secondary rise in ADH whereas a high arginine vasopressin (AVP) level is the primary etiologic event in patients with SIADH [Table 2].

Diuretic-induced hyponatremia: Hyponatremia is common with use of thiazides, begins soon after initiation of thiazides, may be severe and is common in elderly females. Thiazide-induced hyponatremia, occurs due to increased water intake, reduction in diluting ability and water excretion in distal tubule. Sodium plus potassium concentration in urine exceeds that in the plasma, which directly lowers plasma sodium concentration.[10] Loop diuretics cause inhibition of sodium chloride transport in the loop of Henle which prevents the generation of the countercurrent gradient and therefore restricts water retention by ADH. Hence hyponatremia is not common with loop diuretics. Furosemide-related hyponatremia tends to occur after many months of therapy, often when an intercurrent illness develops.

Mineralocorticoid deficiency is another important cause of hypovolemic hyponatremia and may be associated with hyperkalemia.

Euvolemic hyponatremia

It is the most common and accounts for 60% of all cases of hyponatremia. The commonest cause of euvolemic hyponatremia is Syndrome of inappropriate secretion of Anti diuretic hormone (SIADH).[11] Other causes are shown in Figure 2.

SIADH

The criteria necessary for a diagnosis of SIADH were defined by Bartter and Schwartz in 1967.[12] The essential and supporting diagnostic criteria are shown in the Table 1. The final criterion emphasizes that SIADH remains a diagnosis of exclusion and the absence of other potential causes of hypo-osmolality must always be verified.[12,13,14] The causes of SIADH are shown in Tables 3 and 4.

Pathogenesis of hyponatremia in SIADH

Plasma sodium concentration (PNa) is given by ratio of the body's content of exchangeable sodium and potassium (NaE and KE) and total body water (TBW): PNa ≈ NaE + KE/TBW. TBW depends on urine volume. Urine volume cannot be increased in SIADH. This occurs because of defects in Antidiuretic

hormone (ADH, arginine vasopressin) secretion.

Patterns of ADH secretion: In normal individuals, plasma ADH levels is suppressed when the plasma osmolality is below 280mosmol/kg, thus ingested water is excreted and ADH levels increase as the plasma osmolality rises above 280mosmol/kg.

ADH regulation is impaired in SIADH and four different patterns are seen:

- Type A – there is unregulated release of ADH that has no relation to plasma osmolality. Plasma ADH levels are above that required for maximum antidiuresis, so urine osmolality is very high
- Type B –there is a modest and constant leak of ADH.
- Type C- there is downward resetting of osmostat. It is a variant of SIADH in which the plasma sodium concentration is normally regulated and is stable at a lower level (125 -135 meq/L)
- Type D- is the least common. Osmoregulation is normal (i.e. ADH secretion varies appropriately with the plasma osmolality), but the urine is concentrated even with suppressed ADH release. There are 3 mechanisms (a) germ cell mutation in which the V2 vasopressin receptor is activated. (b) Production of antidiuretic compound other than AVP and (3) a postreceptor defect in trafficking of aquaporin-2 water channels, which mediate ADH action.

Exercise-associated hyponatremia

Marathon runners may develop severe hyponatremia due to excessive water intake associated with persistent ADH secretion in some.[24,25]

Low dietary solute intake

Beer drinkers or other malnourished patients (those with low-protein, high water intake diets) have a marked reduction in water excretory capacity despite suppressed ADH. In a normal person ingestion of a normal diet results in the excretion of 900 mosmol of solute per day (primarily sodium, potassium salts and urea). If the minimum urine osmolality is 60 mosmol/kg, the maximum urine output will be 15 L/day (eg. 900 mosmol/day ÷ 60 mosmol/kg = 15 L). In beer drinkers and those who take a very poor diet there is little or no sodium, potassium, or protein in the diet and the carbohydrate load in beer suppresses endogenous protein breakdown and urea excretion. As a result, daily solute excretion is less than 250mosmol. Hyponatremia occurs if daily fluid intake is more than 4 l/day.[26]

Primary polydipsia

Is characterized by increase in thirst and is most often seen in patients with psychiatric illnesses. Normally the thirst threshold is equal to or a few mosmol/kg higher than that for ADH. Hence, ADH is suppressed once ADH threshold is reached. However; in the osmotic threshold for thirst is reduced below the threshold for ADH release. The patients continue to drink until the thirst threshold. However; fall in plasma osmolality suppresses ADH secretion with diuresis. This causes continued stimulation of thirst. Thus normal osmolality is not achieved. As ADH regulation is intact in primary polydipsia they can produce more than 400 to 600 mL of dilute urine per hour, when ADH is suppressed with a minimum urine osmolality of 40 mosmol/kg. Excess water is thus excreted and hence serum sodium concentration is normal or only slightly reduced and hence these patients are usually asymptomatic or may have polydipsia and polyuria. However; they cannot excrete massive water load (400 to 600 mL per hour) which may be seen in psychotic patients or acute water load of 3 to 4l. This may cause fatal hyponatremia even though the urine is maximally dilute.[27]

The cause for defective thirst is not known. In some patients hypothalamic lesions that affect the thirst center, infiltrative diseases such as sarcoidosis can result in primary polydipsia. Patients with polydipsia should be evaluated with a computed tomography or magnetic resonance imaging (MRI) scan of the brain before concluding that excessive water intake is due to a psychiatric cause. There is no specific therapy for primary polydipsia.[28] Limiting water intake rapidly raises the plasma sodium as the excess water is readily excreted. In long term limiting the use of drugs that cause dry mouth, restricting fluid intake and frequent weighing are useful.

Hypervolemic hyponatremia

It is seen in congestive heart failure and cirrhosis of liver, nephrotic syndrome and chronic kidney disease. Even though the plasma and extracellular volumes is increased in heart failure and cirrhosis, there is ADH stimulation as described under pathogenesis. The development of hyponatremia is a poor prognostic sign.

Hyponatremia occurs commonly in both acute and chronic renal failure, because the kidneys cannot maximally excrete excess ingested water. In contrast, hyponatremia is not very common in the nephrotic syndrome unless associated with a substantial decrease in GFR. However, with severe hypoalbuminemia of <2g/dL, intravascular hypovolemia may occur and lead to the nonosmotic release of AVP with subsequent retention of hypotonic fluids. Fluid restriction is the cornerstone of therapy.

Diagnosis of hyponatremia

History and examination

Drug and diet history, history of volume loss i.e. diarrhea, vomitings should be noted.

Determination of volume status i.e. dehydration, oedema, ascites should be carried out.[29] Patients with clinical signs of volume depletion (e.g. orthostatic decreases in blood pressure and increases in pulse rate, dry mucus membranes, decreased skin turgor) should be considered hypovolemic. When available, direct hemodynamic measurements can provide corroboration of the clinical impression. Signs of hypothyroidism or adrenal insufficiency should be noted. Also a detailed examination should be done to detect any CNS or lung lesion.

Investigations

Step 1: Measurement of serum sodium

Ideally by ion specific electrode (ISE) using direct potentiometry (IB).[9,30]

Pseudohyponatremia (falsely low Na with normal plasma osmolality) is not seen if ISE with direct potentiometry method is used. However, many laboratory analyzers that measure sodium with ion-selective electrodes utilize indirect potentiometry in which the plasma sample is diluted before measurement; these analyzers will report a low sodium concentration. Flame photometers may result in low values of serum sodium as they measure the sodium only in aqueous phase.

Step 2: Serum osmolality

It differentiates true, pseudo or translocational hyponatremia [Figure 1]. Calculated serum osmolality may not reflect serum osmolality if other osmotically active solutes are present in the plasma. Hence, serum osmolality should be measured by osmometer, (IB). If osmometer is not available, random blood sugar, serum triglyceride and serum protein should be helpful in differentiating the three types.[1] Each mg increase in blood glucose above 100 mg/dl decreases the serum sodium by 1.6 meq/l. When blood sugar is less than 200 to 300 mg/dl, hyperglycemia has negligible effect on serum sodium concentration. When

serum triglycerides are above 100 mg/dl, for every 500 mg/dl rise in serum triglycerides, fall in serum sodium will be about 1.0 mEq/L. When serum protein is above 8 gm/dl, for every 1 gm/dl rise in serum protein, fall in serum sodium will be about 4.0 mEq/L.

Step 3: Urine osmolality

Urine osmolality can be used to distinguish between impaired water excretion and hyponatremia with normal water excretion [Table 5].

Impaired water excretion (Urine osmolality > 150 mosm/kg).

The normal response to hyponatremia is marked suppression of ADH secretion, resulting in the excretion of a maximally dilute urine with an osmolality below 100 mosmol/kg and a specific gravity ≤1.003. Values above this level indicate an inability to normally excrete free water, most commonly because of persistent secretion of ADH.

Step 4: Urine sodium

Determination of source of sodium loss-renal or non renal is the next step.

This is done by measuring the urinary sodium losses. In patients with hypoosmolal hyponatremia and inappropriate urine concentration, the urine sodium and urine chloride concentrations can be used to distinguish between hypovolemic and euvolemic hyponatremia In hypovolemic hyponatremic patients who have metabolic alkalosis caused by vomiting, the urine sodium concentration may be greater than 20 meq/L, but the urine chloride concentration will be low (less than 20 meq/L).

Clinical assessment of volume status is less accurate than urine sodium.

If initial urine sodium concentration is equivocal, it could be difficult to differentiate true hypovolemia or euvolemic hyponatremia. In this situation serial monitoring of the urine osmolality and urine sodium concentration in response to the administration of 1litre 0.9% NaCl can help clarify the diagnosis.

- If the patient is hypovolemic, 0.9% NaCl should suppress the hypovolemic stimulus to ADH release, promoting the excretion of a dilute urine (urine osmolality usually less than 100 mosmol/kg) and rapid correction of the hyponatremia
- If the patient has SIADH, ADH release occurs independently of the volume status and the urine osmolality will remain elevated following 0.9% NaCl therapy.

In both disorders, the urine sodium concentration will increase with saline therapy, although the increase in hypovolemic patients will not be seen until the hypovolemia is corrected.

Step 5: Urine to serum electrolyte ratio

It is the sum of the urine sodium plus potassium concentrations divided by the serum sodium concentration.

- Ratio < 0.5 (high urine electrolyte-free water)- fluid restriction is adequate
- Ratio > 1 (urine is hypertonic compared to the serum- water restriction is not sufficient and other therapeutic measures are necessary to correct the hyponatremia.[31]

Step 6: Fractional excretion of sodium

Fractional excretion of sodium (FENa) provides an accurate assessment of volume status than the urine sodium alone because it corrects for the effect of variations in urine volume on the urine sodium.

In patients with normal renal function and hyponatremia cut off for FENa is <0.1%.

- <0.1%- hypovolemic hyponatremia
- >0.1%- hypervolemic and normovolemic hyponatremia.

Step 7: Serum uric acid and urea concentrations

Low serum uric acid and urea

- SIADH: The water retention in SIADH is associated with hypouricemia and low BUN. Serum uric acid <4 mg/dL is due to increased uric acid excretion in the urine resulting from reduced proximal sodium and uric acid absorption. Stimulation of the vasopressor V1a receptor also contributes to the uric acid wasting. Water retention also causes low BUN. Thus, in hyponatremia due to SIADH, the blood urea nitrogen (BUN) is usually less than 5 mg/dL. However as urea excretion decreases with aging the absence of a low BUN cannot be used to exclude SIADH in older patients[32,33]
- Hypopituitarism
- Hypervolemia (V1a receptor stimulation) increases urinary urea clearance
- Thiazide diuretic-induced hyponatremia similar reductions in uric acid and urea levels can occur in patients with thiazide diuretic-induced hyponatremia where thiazides are used for water overload.

Normal serum uric acid and urea

- In hypovolemia the levels of urea and uric acid may be normal or high.

Step 8: Acid-base and potassium balance

Evaluation of acid-base and potassium balance may be helpful in some patients.[34]

- Metabolic alkalosis and hypokalemia - diuretic use or vomiting
- Metabolic acidosis and hypokalemia - diarrhea or laxative abuse
- Metabolic acidosis and hyperkalemia - primary adrenal insufficiency in patients without renal failure
- Normal acid base and potassium - in the SIADH
- Mild metabolic alkalosis and normal K- is seen in hypopituitarism because of higher plasma aldosterone levels.

Step 9: Saline infusion

In case of doubt, one can initiate 0.9% NaCl infusion with monitoring of serum sodium and follow-up at 6 to 8 h. Hypovolemic hyponatremia improves with 0.9% NaCl while hyponatremia in SIADH may not be corrected and usually worsens with 0.9% NaCl administration.

Other investigations

Thyroid profile, ACTH and ACTH stimulation tests, CT/MRI brain and imaging of chest are done as needed.

General Guidelines for Treatment

Principles of treatment of hyponatremia

Treatment depends on

- Volume status

- Duration of hyponatremia (whether acute/<48 h or chronic >48 h))
- Presence or absence of symptoms
- Etiology of hyponatremia.[9,30,35,36]

Euvolemic hyponatremia

General treatment

- Acute hyponatemia is generally symptomatic. The risk of brain herniation is high and rapid correction is needed. Acute hyponatremia is common in marathon runners, patients with primary polydipsia and users of ecstasy. These patients have not had time for the brain adaptations to occur. Treatment is recommended with 3% NaCl (1 litre = 513meq Na+). Recent guidelines have suggested giving a bolus of 100ml 3% NaCl IV over 10 min, repeated upto 3 doses till acute symptoms subside. The goal is to provide an urgent correction by 4 to 6 mmol/L to prevent brain herniation. For mild to moderate symptoms with a low risk of herniation, 3% NaCl is infused at 0.5-2 mL/kg/h[1]
- Chronic hyponatremia- It is generally asymptomatic or has mild symptoms. However; it may present with seizures if hyponatremia is very severe.

If chronic hyponatremia is symptomatic (seizures or confusion) or is severe (serum sodium concentration below 125 meq/L aggressive therapy is indicated as for acute hyponatremia. 3% NaCl is recommended with or without vasopressin receptor antagonists.[9,30,35,36] and Initial administration of 3% NaCl therapy is needed to raise the serum sodium by 4-6 mmol above baseline.

Patients with mild symptoms (eg, dizziness, forgetfulness, gait disturbance) should be treated with less aggressive therapy.

- Fluid restriction if the urine to serum electrolyte ratio is less than 0.5
- Among patients with urine to serum electrolyte ratio greater than 1, in whom fluid restriction will not be sufficient to achieve the desired goal, additional therapy includes salt tablets and if necessary, a loop diuretic
- An alternative approach is the initiation of a vasopressin antagonist without fluid restriction.

Rate of correction: In chronic hyponatremia the brain undergoes adaptation and hence the risk of cerebral herniation is very low unlike the risk in acute hyponatremia. Instead very rapid correction can lead to osmotic demyelination syndrome (ODS). Hence, chronic hyponatremia generally needs gradual correction. High risk of ODS is seen esp. if serum sodium is 120meq/L or less or if comorbidities such as alcoholism, liver disease, malnutrition, or severe hypokalemia are present. Apart from rapid rate of correction, ODS may also occur in patients whose hyponatremia “autocorrects” unexpectedly e.g., hyponatremia caused by cortisol deficiency, desmopressin acetate (DDAVP).etc

- In patients with low risk of ODS a maximum 10-12 meq/L increase in serum sodium concentration in 24 h is sufficient to reverse most severe manifestations of acute hyponatremia. Recent guidelines propose a rise of 4 to 8 mmol/day (maximum of 10 to 12 mmol/day)[1]
- In patients with high risk of ODS the serum sodium concentration be raised by a goal of 4 to 6 meq/L per 24 h and by less than 9 meq/L in any 24 h period. Recent guidelines suggest an increase of 4 to 6mmol is sufficient with maximum of 8 mmol/l.[1]

Osmotic demyelination-It is a rare, but severe and sometimes irreversible disorder. It presents with locked in syndrome i.e. quadriparesis with preserved vertical eye movements. This disorder was formerly called central pontine myelinolysis (CPM), but the name was changed because demyelination is more diffuse and does not necessarily involve the pons and.[37,38,39,40] andIn chronic hyponatremia brain adaptation reduces the severity of brain swelling but this adaptation also increase the risk of harm from rapid correction of the hyponatremia leading to ODS. Recently, it has been shown that ODS can be reversed by relowering sodium and giving desmopressin.[1,41]

Equation to estimate efficacy of initial therapy

- The degree to which one liter of a given solution initially raises the serum sodium concentration (SNa) in a hyponatremic patient, without any water or sodium losses in the urine, is estimated from the Adrogué-Madias formula, ie Increase in SNa = (Infusate [Na] – SNa) ÷ (TBW + 1) where TBW is the estimated total body water (lean body weight times 0.5 for women, 0.6 for men). Adrogué-Madias formula cannot be used as the sole guide to therapy; monitoring of the serum sodium concentration is essential in all cases. Potassium added to the solution should be included in the formula (i.e. “Infusate [Na + K]” rather than “Infusate [Na]”) as potassium administration for concurrent hypokalemia can raise the serum sodium concentration
- Another formula was proposed to estimate both the sodium deficit and the direct effect of a given fluid (3% NaCl) on the serum sodium (SNa) concentration, for example:
  Sodium deficit = Total body water (TBW) × (desired SNa – actual SNa)
  However, these formulae have limitations and cannot be used to accurately predict the magnitude of change in serum sodium and frequent measurements are necessary.
- In the current guidelines these formulae are not used. Instead 1ml/kg of 3% NaCl is estimated to raise the serum Na by 1meq/l.

In addition water restriction, salt, urea, demeclocycline and vaptans are used according to the etiology.

Specific treatment for euvolemic hyponatremia

SIADH: It is important to rule out hypothyroidism and glucocorticoid deficiency before diagnosis of SIADH. The treatment of SIADH follows the same principles as mentioned above. Hyponatremia in SIADH is usually chronic and hence slow correction is needed. In cases of chronic hyponatremia or mild symptoms water restriction is the main cornerstone of treatment. Diurectics and vaptans are the other drugs used. In some severe, symptomatic or acute cases 3% NaCl is needed.

3% NaCl: Fluid must be given if the serum sodium concentration must be raised quickly because of symptomatic hyponatremia. The cation concentration of the administered fluid must exceed the cation concentration of the urine. 0.9% NaCl has a limited role in correction of the hyponatremia in SIADH and 3% NaCl is the fluid of choice. The amount of 3% NaCl needed can be calculated as per above formulae. Approximately 1 ml/kg of 3% NS increases the serum sodium by 1meq/l. Careful monitoring of the serum sodium is essential to prevent very rapid correction.

Fluid restriction: The effectiveness of fluid restriction can be predicted by the urine to serum electrolyte ratio as described above. All fluids, not only water, must be included in the restriction; several days of restriction are usually necessary before a significant increase in plasma osmolality occurs; and only fluid, not sodium, should be restricted. Thirst, can be ameliorated by substituting hard candy or ice chips for drinking fluids.

Diuretics: Concurrent use of a loop diuretic is beneficial in patients with SIADH who have a high urine to serum electrolyte (>1). Furosemide inhibits the sodium chloride reabsorption in the thick ascending limb of the loop of Henle and cause more of water loss than sodium loss (urine produced is like ½ normal saline). Thiazides should not be used.

Other drugs used for chronic SIADH are urea, demeclocycline and the vaptans.

Demeclocycline: Causes a nephrogenic form of diabetes insipidus, thereby decreasing urine concentration even in the presence of high plasma AVP levels. Appropriate doses of demeclocycline range from 600 to 1,200 mg/day administered in divided doses. Treatment must be continued for several days to achieve maximal diuretic effects; one should wait 3 to 4 days before deciding to increase the dose. Demeclocycline can cause reversible azotemia and sometimes nephrotoxicity, especially in patients with cirrhosis and should be discontinued if increasing azotemia occurs.

Vaptans: Role of vaptans in euvolemic hyponatremia is discussed below.

Some causes of SIADH can be corrected e.g. self-limited disease (e.g. nausea, pain, surgery), cessation of drugs that cause SIADH and treatment of tuberculosis or meningitis

Primary polydipsia

Fluid restriction is warranted in hyponatremic patients with primary polydipsia in whom increased fluid intake is the primary problem.

Adrenal insufficiency

Glucocorticoid deficiency should be excluded by proper tests. Although glucocorticoid deficiency can be ruled out in some patients with a random or early morning cortisol level >18 mg/dL, failure to achieve this level will require consideration of a cosyntropin stimulation test for a definitive diagnosis. Treatment consists of Glucocorticoids for adrenal insufficiency (suppress ADH). As risk of ODS is high general guidelines for chronic hyponatremia should be followed.

Hypothyroidism

Unless hypothyroidism is severe (ie, symptoms and signs of myxedema or thyroid-stimulating hormone >50 mIU/mL), other causes of hyponatremia should be sought rather than ascribing the hyponatremia to hypothyroidism. Unless the patient has symptoms of hyponatremic encephalopathy, primary treatment of hyponatremia should consist of thyroid hormone replacement at standard weight-based doses; several days may be needed to normalize the serum [Na”].[1]

Psychosis-Antipsychotic drug clozapine is useful in at least some psychotics.

Low solute intake should be corrected.[1]

Exercise induced hyponatremia- it is acute and symptomatic and needs rapid correction with 100 ml boluses of 3% NaCl. Risk of ODS is small.[1]

Hypovolemic hyponatremia

Presentation may be acute or chronic. Mostly it is chronic.[1]

- Sodium chloride, usually as 0.9% NaCl (1l provides 154meq of Na+). Patients need administration of sodium chloride to correct the volume deficit, 3% normal saline is not indicated. K may be added if required. 0.9%NaCl corrects the hyponatremia by two mechanisms: It slowly raises the serum

sodium by approximately 1 meq/L for every liter of fluid infused since 0.9%NaCl has a higher sodium concentration (154meq/L) than the hyponatremic plasma and by correcting the hypovolemia, it removes the stimulus to ADH release

- Gastrointestinal losses- may be acute or chronic. Urine Cl is a better marker for volume status in patients with vomiting instead of Urine Na. Both K and bicarbonate deficits should be corrected along with volume correction
- CSW may present acutely. Moslty 0.9% NaCl is adequate, however, in some cases 3%NaCl may be needed
- Thiazides induced hyponatremia is usually chronic and should be corrected slowly as risk of ODS is high. K should also be supplemented. Patients with thiazide-induced hyponatremia are at high risk for a recurrence and should not be rechallenged with a thiazide
- Mineralocorticoid deficiency associated hyponatremia is chronic and responsds to 0.9% NaCl. Fludrocortisone may be need for long term treatment
- For chronic hyponatremia increased dietary salt is preferred
- Vaptans are not recommended for hypovolemic hyponatremia (see below).

Hypervolemic hyponatremia

- Hypervolemic hyponatremia is seen in CHF and cirrhosis
- Salt administration or 3%NaCl is generally contraindicated for chronic therapy in edematous patients, however may be needed in case of acute symptomatic hyponatremia and can be given as per management of acute symptomatic hyponatremia discussed above
- Water restriction is the mainstay of therapy. Cirrhotics may need severe water restriction (<750 ml/day) which is difficult[1]
- Loop diuretics are the cornerstones of therapy in hypervolemic hyponatremia
- In CHF other therapies used include neurohormonal blockade, angiotensin-converting enzyme inhibitors and β-adrenergic antagonists
- Terlipressin, a V1a receptor agonist, is used to treat hepatorenal syndrome
- Role of Vaptans is discussed below under section on vaptans.

Vasopressin receptor antagonists (Vaptans)

Vaptans act on vasopressin receptors as antagonists. There are multiple receptors for vasopressin (ADH): The V1a, V1b and V2 receptors. The V2 receptors cause antidiuresis, while V1a and V1b receptors cause vasoconstriction and adrenocorticotropic hormone (ACTH) release, respectively. The vasopressin receptor antagonists produce a water loss (aquaresis) without affecting sodium and potassium excretion. Vaptans are the most appropriate physiological approach to treat hyponatremia as they do not deplete electrolytes and restriction of fluids is not needed. They do not stimulate the neurohormonal system and cause no renal impairment.

There are both oral and IV preparations available.

Nonselective (mixed V1A/V2): Conivaptan. Intravenous

V1A selective (V1RA): Relcovaptan.

V1B selective (V3RA): Nelivaptan,

V2 selective (V2RA): Lixivaptan, Moxavaptan, Satavaptan, Tolvaptan.

Only tolvaptan and conivaptan are currently available in India.

I Vaptans in euvolemic hyponatremia

Treatable causes of Euvolemic Hyponatremia should be excluded e.g. hypothyroidism, glucocorticoid deficiency etc.

Vaptans are not recommended as single agents for the treatment of hyponatremic emergencies but could be used as dose-sparing adjunctive therapy with 3% NaCl.

Vaptans are useful for chronic hyponatremia. Vaptans are used in addition to fluid restriction and sodium chloride administration.[42,43]

Tolvaptan: The efficacy of oral tolvaptan was demonstrated in multicenter trials (SALT-1 and SALT-2) [44,45] in 448 patients with hyponatremia caused by SIADH. Tolvaptan significantly increased serum sodium concentration. Even with modest sodium improvement there was significant increase in mental scores. But the effect was not clinically significant and long-term efficacy was doubtful as the patients were followed up for only 30 days. In SALT-2 hyponatremia recurred after discontinuing of Tolvaptan. In SALTWATER trial (Safety and sodium Assessment of Long-term Tolvaptan With hyponatremia Trial to gain Experience under Real-world conditions) the mean serum sodium in treated group was 135 meq/L versus 131meq/L at baseline in patients with SIADH,. and. At 50 weeks, the serum sodium concentration normalized in approximately 60% of the patients. In a multicenter trial (TEMPO 3:4)[46,47] a greater than 2.5-fold increase in liver enzymes was more common is study group versus placebo. Thus liver function tests should be performed initially and LFT should be repeated three to four months after initiating therapy and then again at six-month intervals. If liver injury is suspected, tolvaptan should be discontinued. Recently FDA has recommended Tolvaptan use but not for greater than 4 wks.[48] Tolvaptan treatment must be initiated in the hospital so that the rate of correction can be monitored carefully. Patients with a serum [Na”] <125 mmol/L are eligible for therapy with tolvaptan as primary therapy; if the serum [Na”] is >125 mmol/L, tolvaptan therapy is only indicated if the patient has symptoms that could be attributable to the hyponatremia and the patient is resistant to attempts at fluid restriction. The starting dose of tolvaptan is 15mg on the first day and the dose can be titrated to 30mg and 60 mg at 24-h intervals if the serum [Na”] remains <135 mmol/L or the increase in serum [Na”] is <5 mmol/L in the previous 24 h. Serum [Na”] concentration should be measured during the active phase of correction of the hyponatremia at a minimum of every 6 to 8 h. Fluid restriction should not be used during the active phase of correction, thereby allowing the patient's thirst to compensate for vigorous aquaresis. Appropriate caution should be exercised in patients treated with tolvaptan for hyponatremia for extended periods (e.g. >30 days) due to risk of liver damage, but this decision should be based upon the clinical judgment of the treating physician. Patients who are refractory to or unable to tolerate or obtain other therapies for hyponatremia and in whom the benefit of tolvaptan treatment outweighs the risks, remain candidates for long- term therapy with tolvaptan; but in such cases, liver function tests should be monitored carefully and serially (i.e. every 3 m) and the drug discontinued in the event of significant changes in liver function tests (i.e. 2 times increase in ALT beyond upper limit).

Conivaptan is FDA approved for euvolemic hyponatremia in hospitalized patients. It is available only as an intravenous preparation and is given as a 20-mg loading dose over 30 min, followed by a continuous infusion. Generally, the 20-mg continuous infusion is used for the first 24 h. If the correction of serum [Na”] is felt to be inadequate (e.g. <5 mmol/L), then the infusion rate can be increased to 40 mg/d. Therapy is limited to a maximum duration of 4 days because of drug-interaction effects with other agents metabolized by the CYP3A4 hepatic isoenzyme. Serum [Na”] concentration is measured frequently during the active phase of correction of the hyponatremia-a minimum of every 6 to 8 h, but more frequently in patients with risk factors. Although vaptans are not contraindicated with decreased renal function, these agents generally will not be effective if the serum creatinine is >2.5 mg/dL

II Vaptans in hypervolemic hyponatremia

CHF

Vaptans can be used in CHF patients for management of fluid overload and/or hyponatremia after water restriction and diuretics have been tried. Hyponatremia in CHF is chronic and should be corrected till serum Na is normal and symptoms improve. The level of serum Na should be normalized so that diuretic therapy for CHF can be optimised. In some studies, hyponatremia was associated with increased mortality and increased rate of re-hospitalization in patients of acute heart failure.[49,50] Short-term trials like EVEREST (Efficacy of Vasopressin antagonist in hEart FailuRE outcome Study with Tolvaptan)[51] and ACTIV in CHF (Acute and Chronic Therapeutic Impact of Vasopressin antagonist in Congestive Heart Failure)[52] showed a rapid increase in serum sodium and improvement in hemodynamic parameters with vaptans, however long-term trials have failed to demonstrate a favorable effect on morbidity and mortality. Further studies of the Vaptans are necessary to determine whether serum sodium normalization will be translated into a better long-term prognosis in patients with CCF.

Cirrhosis

Vaptans can be used in cirrhotic patients for management of fluid overload and/or hyponatremia after water restriction and diuretics have been tried. However Tolvaptan has been found to be hepatotoxic and hence USFDA has limited their use only in those hyponatremic patients with end-stage liver disease who are awaiting imminent liver transplantation, who are at little risk of added hepatic injury and will benefit from correction of hyponatremia before surgery to decrease the risk of ODS postoperatively. In earlier studies the patients with cirrhosis were found to have improved serum sodium levels with vaptans however therewas no clear difference between Vaptans and control groups regarding mortality, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, or renal failure.[53] Conivaptan lowers the blood pressure and increases the risk of variceal bleeding in patients with cirrhosis. Hence is contraindicated in cirrhosis. Satvaptan was found to maintain sodium levels long term in cirrhotics however it's use is also limited.[54]

Contraindications to vaptans-Vasopressin receptor antagonists should not be used in hyponatremic patients who are volume depleted. Vaptans should not be used to treat the type of euvolemic hyponatremia caused by emetic stimuli or secondary adrenal insufficiency and they are ineffective in the vasopressin-independent form of SIADH (caused by an activating mutation of the V 2 receptor). They are ineffective where AVP levels are appropriate, for example, cerebral salt wasting and psychogenic polydipsia.

Adverse effects

Thirst, Dryness of mouth, Orthostatic hypotension, Encephalopathy.

Acute Kidney Injury, Hyperkalemia and Conivaptan is a potent inhibitor of cytochrome P450 3A4 (CYP3A4), which could lead to serious drug-drug interactions. Tolvaptan has less potential for drug-drug interactions. Coadministration of conivaptan with potent inhibitors of (CYP3A4), such as ketoconazole, itraconazole, clarithromycin, ritonavir and indinavir is contraindicated.

Weight, serum sodium, Blood pressure, liver functions should be monitored every 15 days for 2-3 months then monthly. Serum potassium and kidney functions should be monitored regularly.

Conclusion

Hyponatremia is a frequently encountered problem in clinical practice and is an important cause of morbidity and mortality. Establishment of etiology and appropriate treatment improves outcome. A knowledge of recent guidelines of treatment and the appropriate use of vaptans is essential for all clinicians for proper diagnosis and management.

Footnotes

Source of Support: Nil

Conflict of Interest: No.

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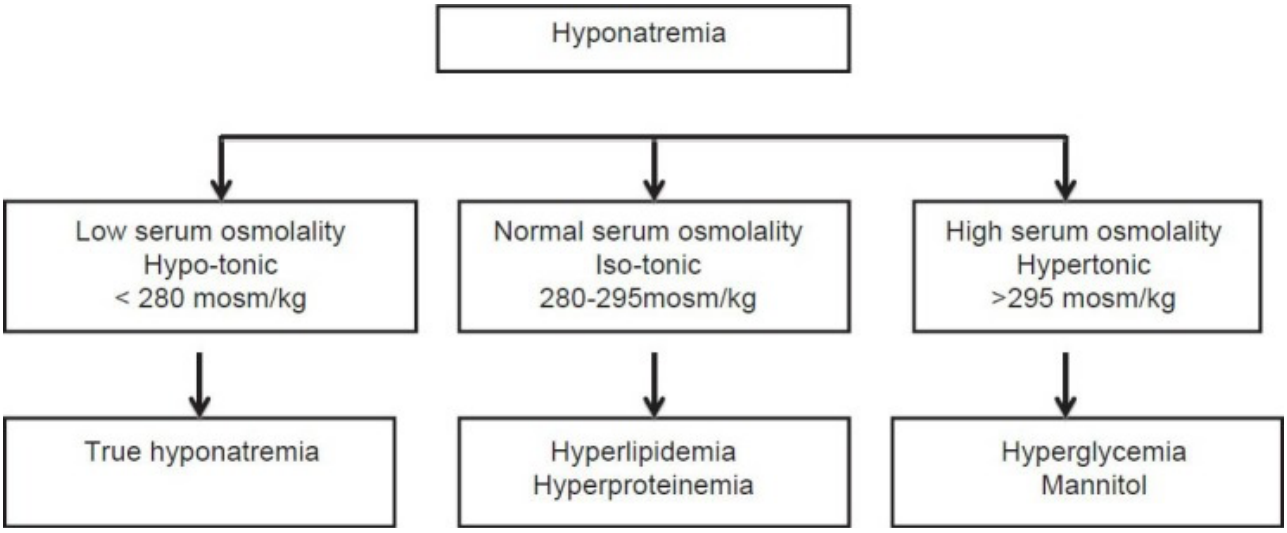
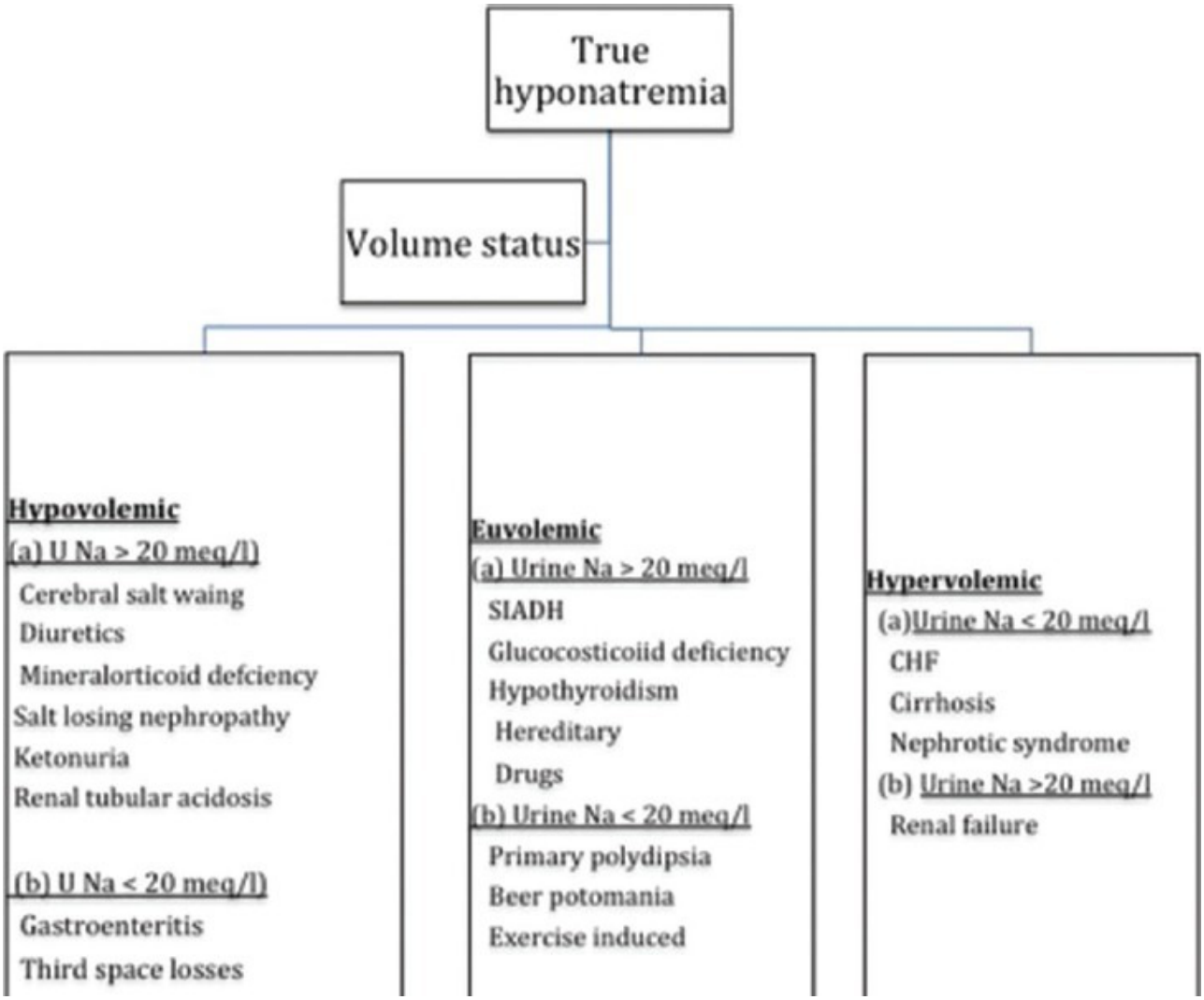
Figures and Tables

Figure 1



Types of hyponatremia

Figure 2



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Approach to hyponatremia

Table 1

Diagnostic Criteria of SIADH

Schwartz diagnostic criteria for SIADH
Decreased measured serum osmolality (<275 mOsm/kg H_2O)
Clinical euvolemia
Urinary osmolality >100 mOsm/kg H_2O
Urinary [Na+] >40 mmol/L with normal dietary sodium intake
Normal thyroid and adrenal function.
Normal renal functions
Exclude use of diuretic agents within the week prior to evaluation
No hypokalemia, no acid base disorders
Supporting diagnostic criteria for SIADH
Serum uric acid<4 mg/dL
Blood urea nitrogen <10 mg/dL
Fractional sodium excretion >1%; fractional urea excretion >55%
Failure to improve or worsening of hyponatremia after 0.9% saline infusion
Improvement of hyponatremia with fluid restriction

SIADH: Syndrome of inappropriate secretion of anti diuretic hormone

Table 2

Differential diagnosis of SIADH

	SIADH	Cerebral salt wasting
Pathogenesis	Inappropriate ADH secretion	Increased Brain natriuretic peptide
Hyponatremia	Yes	Yes
Urinary Sodium	High	High
ECF volume	Increased	Decreased
BP and CVP	Normal	Normal/low normal
Urine volume	Normal/low	High
Blood urea	Normal/low	High
BUN/creatinine ratio	Decreased	Increased
Plasma uric acid	Decreased	Normal or decreased
Hematocrit	Normal	Increased
Treatment	Fluid restriction+ Furosemide	Normal saline+ Fludrocortisone rarely

SIADH: Syndrome of inappropriate secretion of anti diuretic hormone, BUN: Blood urea nitrogen, BP: Blood pressure, ECF: Extracellular fluid, CVP: Central venous pressure

Table 3

Etiology of SIADH

CNS disturbances
Stroke
Hemorrhage
Infection
Trauma
TB
Psychosis[15]
Malignancies (Ectopic production of ADH)
Small cell carcinoma of lung, other lung tumors
Head and neck cancer
Olfactory neuroblastoma (esthesioneuroblastoma)
Extrapulmonary small cell carcinomas[16]
Drugs
Surgery[21]
Pulmonary disease
Pneumonia (viral, bacterial, tuberculosis)
Asthma
Atelectasis
Acute respiratory failure
Pneumothorax
Hormone deficiency
Hypothyroidism[22]
Hypopituitarism[23]
HIV
Hereditary SIADH

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Table 4

Drugs causing SIADH

Drugs (Enhance ADH release or effect)
Anti-diabetic drugs
Chlorpropamide
Anti epileptic drugs
Carbamazepine, oxcarbazepine
Sodium valproate
Selective serotonin reuptake inhibitors (eg, fluoxetine, sertraline)
Anti cancer drugs
Vincristine, vinblastine, vinorelbine
Cisplatin, thiothixene
Melphalan, ifosfamide, methotrexate
Cyclophosphamide- intravenous
Antipsychotic drugs
Thioridazine
Haloperidol
Amitriptyline
Monoamine oxidase inhibitors
Pain killers
Opiates
Nonsteroidal antiinflammatory agents
Exogenous hormone administration
Vasopressin, desmopressin (dDAVP) or oxytocin
Miscellaneous
Interferon-alpha, interferon-gamma
Bromocriptine

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Table 5

Urine osmolality for differential diagnosis of hyponatremia

High urine osmolality>150 mosm/kg	Low urine osmolality<150 mosm/kg
Hypovolemic hyponatreima	Hypovolemic hyponatremia
Salt depletion	Acute diuretic use
Cerebral salt wasting	
Adrenal insufficiency	
Euvolemic hyponatremia with high urine Na	Euvolemic hyponatremia
SIADH	SIADH (reset osmostat variety)
	Beer potomania
	Exercise induced hyponatremia
	Primary polydipsia

SIADH: Syndrome of inappropriate secretion of anti diuretic hormone