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Critical review

Sodium disorders in critically ill neurologic patients: A focus on pharmacologic management

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Abstract

Introduction

Dysnatremias are common in neurocritically ill patients and optimizing management strategies is important for patient outcomes. Well-defined diagnostic criteria and standardized treatment approaches do not exist for these conditions, posing a challenge to providers. The aim of this paper is to discuss pharmacologic treatment options for the most common sodium disorders seen in critically ill neurologic patients: syndrome of inappropriate antidiuretic hormone, cerebral salt wasting, and central diabetes insipidus.

Conclusion

Proper treatment of dysnatremias necessitates an accurate diagnosis. In addition, prudent selection of therapeutic strategies and diligent monitoring are important steps to preventing potentially fatal consequences as a result of contrasting treatment strategies for the various types of sodium disorders. A keen understanding of the pharmacotherapy used to treat these disorders is critical to the management of these patients.

Introduction

Disorders of sodium regulation are frequently encountered in critically ill patients. Regardless of etiology, dysnatremias are associated with significant morbidity, mortality, and increased hospital length of stay[1].

Diagnostic challenges arise from the multitude of dysnatremic aetiologies in combination with the ambiguity of interpreting related laboratory values and patient symptoms.

The management of sodium disorders is further complicated by the paucity of well-designed clinical trials, resulting in widely varied treatment strategies. This review focuses on the evidence-based management of patients with the syndrome of inappropriate antidiuretic hormone (SIADH), cerebral salt wasting (CSW), and diabetes insipidus (DI), with emphasis on the pharmacologic treatment options. These three conditions are the most common dysnatremias and the most challenging to diagnose in neurocritically ill patients.

Discussion

Syndrome of Inappropriate Antidiuretic Hormone

Introduction and Pathophysiology

SIADH is characterized by excessive release of antidiuretic hormone (ADH), also known as vasopressin, which serves as the primary regulator of urinary free water excretion. The actions of ADH are mediated by vasopressin receptors (V2) in the renal collecting tubules, leading to excess water reabsorption and impaired free water excretion. Increased release of ADH coupled with excess fluid intake result in increased extracellular fluid and hyponatremia without clinical fluid overload[2,3].

Aetiology

The most common causes of SIADH are malignancy, pulmonary diseases, disorders of the central nervous system, and medications. (Table 1) Malignancies can directly (located on the pituitary gland) or indirectly (located outside of the central nervous system, such as the lung) increase secretion of ADH or ADH-like substances. Additionally, stroke, neurologic infection, traumatic brain injury, and pneumonia can cause SIADH. Some medications can stimulate the release of ADH or enhance its actions[4,5] (Table 1).

Diagnosis

Increased ADH release causes expansion of extracellular volume and a decrease in urine volume and effective serum osmolality. Key features for the diagnosis of SIADH include (assuming normal renal function and salt intake) effective serum osmolality of < 275 mOsm/kg H2O, urinary osmolality of > 100 mOsm/kg and urine sodium concentrations > 30 mEq/L. Absence of signs of volume depletion or excessive volume overload are additional key features of SIADH. SIADH can also be associated with low uric acid levels (< 4 mg/dL) and low blood urea nitrogen (BUN) concentrations (< 5 mg/dL) while serum creatinine, potassium, and acid-base concentrations remain within normal limits. (Table 2) It is important to note that SIADH is a diagnosis of exclusion; therefore, other causes of euvolemic hyponatremia such as hypothyroidism, adrenal insufficiency, and diuretic-induced hyponatremia must first be excluded[4,5].

Management

Management of SIADH should be directed by the severity of hyponatremia, duration, and presence of symptoms. Treating the underlying cause of SIADH is the only definitive treatment.

Acute cases of hyponatremia, defined as < 48 hours, should be corrected[1]. Severe, symptomatic hyponatremia can be managed with hypertonic saline (3%), at a rate of 0.5-2 mL/kg/hr with goal sodium correction of no more than 12 mEq/L in 24 hours or 18 mEq/L in

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Critical review

48 hours[1], although initial infusion rates are controversial[4,6,7]. Such therapy warrants close monitoring of serum sodium levels.

For chronic SIADH or after the correction of the acute phase, fluid restriction should be implemented. The volume of fluid restriction can be determined using the ratio of combined urinary sodium and potassium divided by serum sodium[7]. (Table 3) Other equations exist for determining the amount of fluid restriction; however, providers typically restrict the patient to 1-1.5 L per day in clinical practice. In addition to fluid management, there are pharmacological agents used for hyponatremia associated with SIADH. Dosing and additional pharmacologic detail of these agents can be found in table 4.

Urea is an osmotic diuretic that enhances water flow from tissues into the interstitial fluid and plasma, thereby increasing serum osmolality which enhances diuresis and solute-free water excretion in SIADH. In seven patients with SIADH and a serum sodium < 135 mEq/L, oral urea restored serum sodium concentrations to a mean of 136 mEq/L and urine osmolality to a mean of 652 mEq/kg after one week of therapy[8]. Urea may be an effective adjunct to fluid restriction[9].

Demeclocycline, a tetracycline antibiotic has been used in patients with malignancies to manage SIADH. Treatment with demeclocyline led to increases in serum sodium concentrations within 5 to 14 days[10,11].

The response to demeclocycline can be variable among patients[9]. Interestingly, demeclocyline has the potential to induce nephrogenic diabetes insipidus and should be carefully monitored.

Lithium, a mood-stabilizing agent has also been used to treat SIADH. Studies comparing demeclocycline to lithium suggest superiority of demeclocycline in treating SIADH and its ability to decrease the need for fluid restriction[12]. Lithium also has the potential to induce nephrogenic diabetes insipidus.

Vasopressin receptor antagonists (VRA), also known as "Vaptans" antagonize V2 receptors in the distal nephron, preventing antidiuresis, increasing solute-free water excretion and thereby increasing serum sodium concentration. Selective V2 receptor antagonists include tolvaptan, lixivaptan and satavaptan, while conivaptan is a non-selective V1a and V2 receptor antagonist and the only one available intravenously. Tolvaptan and conivaptan are the only FDA-approved VRAs in the U.S.

VRAs are contraindicated in hypovolemic hyponatremia because of their aquaretic properties. Fluid restriction at the initiation of a VRA can lead to overcorrection of serum sodium concentrations and is therefore not advised. VRAs should be used judiciously and monitored closely in cases where overcorrection could lead to further complications such as in the case of subarachnoid hemorrhage patients with vasospasm. In the SALT-1 and SALT-2 trials[13], tolvaptan studied in the management of euvolemic and hypervolemic hyponatremia (defined as Na < 135mEq/L) in patients with CHF, cirrhosis and SIADH, was shown to increase serum sodium concentrations during the first 4 days and at 30 days of therapy.

In a follow-up analysis[14] focusing on the subset population with hyponatremia secondary to SIADH (n=110), the serum sodium correction to > 135 mEq/ L was achieved in the tolvaptan group within 3-4 days and the effect was sustained throughout the treatment duration. Withdrawal of tolvaptan resulted in the return of hyponatremia within 7 days. Of all tolvaptan-treated patients, 5.9% experienced an overly rapid sodium correction exceeding current correction recommendations of 10-12 mEq/L/day, but without adverse consequences[15].

Similar efficacy and safety were demonstrated in the extension study SALTWATER with long-term tolvaptan therapy with a mean duration of 701 days[16].

Intravenous conivaptan was studied in 84 patients with euvolemic and hypervolemic hyponatremia caused primarily by CHF and SIADH, significantly increased serum sodium by the end of the 4-day treatment[17]. In a retrospective study in 18 patients diagnosed with SIADH, conivaptan was associated with an absolute increase in serum sodium concentration by ≥ 4mEq/L 24hrs- post infusion start and a mean urine osmolality decrease of 45.9 +/- 28.8% from baseline in all patients[18]. The optimal place in therapy for the VRA class of medications remains to be determined.

Table 1: Common Etiologies of SIADH (1).

CNS disorders
· Infections/inflammation
· Hemorrhage
· Traumatic brain injury
· Guillain-Barre Syndrome
· Ischemic Stroke
Pulmonary Disorders
· Infections
· Cystic fibrosis
· Asthma
Malignancy
· CNS tumors
· Carcinoma (lung, gastrointestinal)
· Lymphoma
· Sarcoma
Medications Stimulating the Release of ADH
· SSRIs
· TCAs
· Carbamazepine
· Phenytoin
· Valproic Acid
· Cytotoxins (Vincristine, Cyclophosphamide)
· NSAIDs
· Antipsychotics
· Narcotics
Medications Potentiating the Effect of ADH
· Desmopressin
· Vasopressin
· Oxytocin
· Prostaglandins
Other Causes
· HIV
· Hereditary
· Chronic inflammation
· Prolonged exercise
· Nausea and Vomiting
· Pain
· Idiopathic

Cerebral Salt Wasting

Introduction and Pathophysiology

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CSW is a hyponatremic state characterized by a renal loss of sodium and a decrease in extracellular fluid volume in the setting of neurologic conditions and normal renal function[19].

The exact pathophysiology underlying the development of CSW is not entirely understood. Some experts believe that CSW and SIADH are part of a clinical spectrum in neurological diseases and may actually be the same clinical entity[20]. Others believe that CSW is over diagnosed[1].

Proposed mechanisms include neurological injury causing direct release of atrial and brain natriuretic peptides (ANP and BNP) from damaged brain[21] and diminished[21,22] or increased sympathetic signalling disrupting neural input to the proximal tubule that regulates sodium reabsorption[20]. More recently it has been found that natriuretic peptide levels may not correlate with the development of hyponatremia in subarachnoid haemorrhage (SAH) patients[19,23], and some studies have shown no increases in ANP in this patient population[20].

In general, obtaining biomarker concentrations to assist with determining the aetiology of hyponatremia is not supported by published literature[15]. Alternative hypotheses for the pathophysiology of CSW involve the release of adrenomedullin (DNP), a more recently discovered natriuretic peptide[21].

Aetiology

CSW is typically encountered in neurosurgical patients or patients with intracranial disease or injury. (Table 5) CSW is not thought to be drug-induced unlike many cases of SIADH. Hyponatremia with CSW typically manifests within the first week of neurologic injury, and is often difficult to diagnose secondary to the common presence of other causes of hyponatremia in neurologically ill patients including SIADH[21] (Table 6).

Table 2: Physiological Changes due to Salt Disorders ([1,2,3,4,5,6]).

	SIADH	CSW	DI
Serum Na (mEq/L)	<131-135	< 131	>145
Serum Osmolarity (mOsm/kg)	<280	< 280	>296
Serum uric acid	Normal or Reduced	Reduced	Increased
Serum bicarbonate	Reduced	Increased	Neutral or Increased
Plasma Volume	Neutral or increased.	Reduced	Reduced
Urine Na (mEq/L)	> 30	>>30	<30
Urine Osmolality (mOsm/kg)	≥ 100	≥ 100	< 100
Urine Output	Normal or reduced	Normal or elevated	Elevated
Signs and Symptoms of Dehydration	None	Present (i.e. dry mucous membranes, thirst, prolonged capillary refill, diminished skin turgor, absence of jugular venous distention)	None or present
CVP	Same or slightly elevated (6-10 mmHg)	Reduced (< 6 mmHg)—may not be accurate in ventilated patient	Reduced
Stroke Volume Variation	Normal (< 10%)	Increased (> 10%)	Increased (>10 %)
Hematocrit	Normal	Normal or Increased	Normal or increased
Blood urea nitrogen and serum creatinine	Normal or decreased	Normal or Increased	Increased
Blood pressure	Normal	Normal or orthostatic hypotension	Normal or orthostatic hypotension
Total Body Weight	Same or increased	Reduced	Same or reduced

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Diagnosis

While a universally accepted standard for diagnosing CSW remains elusive, CSW is classically characterized by hypovolemia with hyponatremia as opposed to a euvolemic hyponatremia seen in patients with SIADH. Both conditions result in decreased serum osmolality, decreased serum sodium concentration, and inappropriately concentrated urine[15].

The concentrated urine sodium seen in CSW is a result of the disproportionate loss of sodium to water[21]. Evaluation of urine electrolytes offers no diagnostic value in differentiating between these two conditions which is further complicated by the fact that many neurocritically ill patients receive hypertonic saline for cerebral oedema[20]. The most distinguishing feature of CSW is decreased volume status which may result in elevations in haematocrit, serum creatinine, and blood urea nitrogen secondary to low effective arterial blood volume; however, these particular laboratory findings are not necessarily present in all patients (Table 2). Central venous pressure (CVP) is decreased while stroke volume variation (in mechanically ventilated patients) would be increased secondary to a volume depleted state. The primary distinguishing clinical features consistent with CSW are postural changes in blood pressure or heart rate resulting from contracted extracellular fluid volume[19].

In critically ill patients that cannot be mobilized, it may be prudent to consider CVP or SVV and 24-hour fluid balance to determine the extracellular fluid status. A 24-hr fluid-restriction trial may be helpful in distinguishing CSW from SIADH if deemed safe.

Management

The cornerstone to the management of CSW is the replenishment of both sodium and water losses with 0.9 % sodium chloride which is typically used first-line for volume repletion; however, hypertonic sodium chloride may be required for acute, neurocritically ill patients experiencing cerebral oedema or increased intracranial pressures.

Overall, the aggressiveness of the treatment strategy should be determined by the severity of symptoms with conscious consideration of the potential adverse effects of intervention[9,15]. Hypertonic saline (HTS) can be advantageous in patients with negative fluid balance and intracranial hypertension since HTS has intravascular volume expanding properties and the ability to induce a hypernatremic state.

In patients who are severely volume depleted, ongoing administration of both isotonic and hypertonic saline can be considered. Sodium chloride tablets and fludrocortisone are also treatment options in the management of CSW and have most utility in less severe patients or when weaning hypertonic saline. Again it is important that patients receive adequate volume repletion with these therapies. Fludrocortisone has been shown to reduce natriuresis and the risk of vasospasm in hyponatremic SAH patients[20]. According to three controlled trials, fludrocortisone has been shown to correct the sodium balance and reduce the need for fluid administration in patients with SAH[24,25,26]. The guidelines for the critical care management of patients following SAH suggest considering the early use of fludrocortisone or hydrocortisone to limit hyponatremia and natriuresis[27]. More detail on the therapies used in managing CSW can be found in table 7.

In managing CSW, diagnosis and monitoring are paramount. Therapies such as fluid restriction and vasopressin receptor antagonists, which are commonly utilized in SIADH, can be detrimental in a severely volume-depleted patient[28]. For example fluid restriction of the SAH patient with CSW has been shown to result in increased risk of delayed ischemic deficits and mortality[21]. Additional management strategies that should be avoided are administration of hypotonic fluids, free water, diuretics, and antidiuretic hormone therapy (vasopressin and desmopressin). Serum sodium should be monitored every 4 to 6 hours acutely, and should not be repleted faster than 8-10 mEq/L within 24 hours to avoid the risk of osmotic demyelination syndrome, a rare adverse effect.

Table 3: Daily Fluid Intake for Patients with Chronic SIADH [1].

Urinary[Na^+] and [K^+]/ serum [Na^+]	Fluid intake (ml/day)
>1	<500
1	500-700
<1	<1000

1. Hannon MJ, Thompson CJ. The syndrome of inappropriate antidiuretic hormone: prevalence, causes and consequences. Eur J Endocrinol. 2010;162 Suppl 1:S5-12.

Central Diabetes Insipidus

Introduction and Pathophysiology

DI is defined as an inability to conserve and maintain an appropriate free water level which is manifested as polyuria (urine volume in excess of 40 mL/kg/24 hours)[29]. Absence of ADH stimulation of the V2 receptors results in impermeability of the collecting ducts to water thus generating large volumes of hypo-osmolar urine (< 100 mOsm/kg)[29]. In addition to low urine osmolality, the urine specific gravity is low while plasma osmolality and serum sodium are elevated[30,31] (Table 2).

DI is either caused by a deficiency in plasma ADH resulting from inadequate synthesis, release, or transport from the hypothalamus (central DI) or an inadequate renal response (nephrogenic DI)[29]. The severity of DI varies based on the degree of inadequate ADH secretion or action, resultant fluid intake, and solute load. Because fluid intake and urine output are typically proportional, distinct signs of fluid imbalance in adults are rare. However, severe dehydration and hypernatremia can ensue if the thirst mechanism is impaired or free access to water is limited[29].

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Table 4: Pharmacological Therapy for SIADH.

Medication	Mechanism of Action	Typical Adult Dose	Pharmacokinetic Properties	Adverse effects	Comments
Urea	Induces osmotic diuresis and enhances water diuresis	10-40 g daily or 0.5-1 g/kg/day via gastric tube	**Metabolism:**Systemic with active metabolites including ammonia and carbon dioxide **Excretion:** Renal **Elimination half-life:** 1.17 hr	Taste, abortifacient	-Give oral formulation with orange juice
Demeclocycline (unlabeled use)	Induces nephrogenic diabetes insipidus. Inhibits cyclic adenosine monophosphate	600-1200 mg po daily	**Absorption:** Time to peak concentration with oral: 4 hr Food reduces absorption by > 50% **Distribution:** 40-90% protein binding **Excretion:** Biliary, 44% renal, 13-46% fecal as active drug **Elimination half-life:** 10-16 hr	Photosensitivity	
Lithium	Induces nephrogenic diabetes insipidus	600-900 mg po daily	**Distribution:** Vd: 0.7-1.4 L/kg, no protein binding **Metabolism:** Almost entirely renal **Excretion:** 89-98% renally excreted **Elimination half-life:** 14-24 hr	Acne, gastritis, nausea, hyopothyroidism, thirst, leukocytosis, hyperreflexia, nephrotoxicity	-Requires therapeutic drug monitoring – narrow therapeutic index -Elimination half-life may be prolonged in patients on long-term therapy
Conivaptan	Arginine vasopressin (AVP) V1A and V2 selective antagonist inhibiting vasopressin binding to liver V1A and kidney V1 and V2 receptors	Loading dose: 20 mg IV over 30 minutes; Continuous IV infusion: 20 mg/day (0.83 mg/hr) x up to 4 days- may increase to max of 40 mg/day (1.7 mg/hr)- total duration not to exceed 4 days	**Metabolism:** Extensive hepatic viaCYPP3A4 **Excretion:** 83% fecal (changed), 12% renal changed and 1% renal unchanged **Elimination half-life:**5 to 8 hr	Orthostatic hypotension, fever, hypokalemia, injection site reactions	-Initiate inpatient with close monitoring -Adjustments required for reduced clearance and hepatic dysfucntion -Central line preferred to decrease risk of phlebitis; peripheral line must be rotated every 24 hrs -Bolus dosing no more frequent than every 12 hours is associated with less infusion site reactions
Tolvaptan	Selective vasopressin V2 receptor antagonist, increases urine water excretion resulting in increased free water clearance, decreased urine osmolality, and increased serum sodium concentration	15-30 mg po daily in the morning; maximum 60 mg daily	**Absorption:** Time to Tmax: 1.75-4 hr, 40% bioavailability, food has no effect **Distribution:** Vd 3 L/kg, 99% protein bound **Metabolism:** Extensive hepatic via CYP3A4 **Excretion:** Non-renal **Elimination half-life**2.8-12 hr NG tube administration results in a 25% reduction in AUC and modest reduction in Cmax; 24-hour urine output was reduced by only 2.8% ;therefore, crushing 15mg tablets appears to be an acceptable alternative route of administration	Nausea, xerostomia, pollakiuria, polyuria, thirst	-D/C previous fluid restriction and drink fluids freely -Used for both acute and chronic hyponatremia (1-2 years w/o tachyphylaxis)

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Table: 5 Common Etiologies of CSW[1].

· Aneurysmal SAH · Meningitis · Transphenoidal pituitary surgery · Traumatic brain injury · Malignancies · Glioma · Primary CNS lymphoma

1. Yee AH, Burns JD, Wijdicks EF. Cerebral salt wasting: patho-physiology, diagnosis, and treatment. Neurosurg Clin N Am. 2010; 21(2):339-52.

Table: 6 Example Mechanisms of Medication-Related Causes of Hyponatremic states in Neurocritical care patients[1].

Calcium channel blockers	Nimodipine—activation of ANP and inhibition of aldosterone which can cause or worsen hyponatremia
Triple H therapy (Hypertension, Hypervolemia, Hemodilution)	Administration of significant amounts of isotonic fluid increases extracellular fluid volume which activates natriuretic peptides and suppresses aldosterone
Vasopressors	Pressure diuresis and natriuresis from activation of the adrenergic system

1. Kirkman MA, Albert AF, Ibrahim A, Doberenz D. Hyponatremia and brain injury: historical and contemporary perspectives. Neurocritical care. 2013;18(3):406-16.

Aetiology

The aetiology of central DI may be classified as primary or secondary (Table 8). The majority of central DI cases are considered idiopathic[29].

Trauma, surgery, or primary or metastatic tumours result in damage to the hypothalamoneurohypophyseal region. Central DI following pituitary surgery occurs in approximately 18.5% of cases and can exhibit a transient, permanent, or triphasic pattern. Transient DI accounts for the majority of DI cases following surgery, and manifests as an abrupt onset of polyuria and polydipsia which resolves over days to weeks. Permanent DI manifests similarly, but does not typically resolve and may require lifelong treatment while triphasic DI consists of an initial phase of polyuria and polydipsia that resolves during the first week, followed by SIADH in the second week, and finally prolonged or permanent DI[30,31]. Familial (genetic) central DI is rare[29].

Diagnosis

The diagnosis of DI should begin with a urine osmolality and volume assessment over 24 hours to confirm hypotonic polyuria[29]. Central DI results in low urine osmolality (< 300 mOsm/kg H20) with elevated serum osmolality (> 296 mOsm/kg H20). Fluid restriction and desmopressin (DDAVP) response tests may be performed to distinguish central from nephrogenic DI[29,32]. DDAVP is a synthetic analog of ADH, therefore central DI can be distinguished from nephrogenic DI by observing a rise in urine osmolality from baseline 1-2 hours after 1 mcg of DDAVP is administered IV/SQ[29]. Magnetic resonance imaging may also be useful in distinguishing central from nephrogenic DI[29].

Management

This section will focus on the management of central DI for which the treatment of choice is DDAVP (Table 9). Whether used for acute or chronic treatment, low doses should be used initially and titrated to symptom reduction[32]. Generally, urine output will decrease 1-2 hours after DDAVP is administered, and the duration of effects will vary between 6-24 hours. Based on the patient's response, doses may be adjusted every 24 hours, and increasing the dose of DDAVP will increase the duration of antidiuretic affects. Although up to 30 percent of patients with DI can be maintained with once-daily dosing of DDAVP, some patients may require supplemental doses during the titration phase until an optimal dose is established[33].

Continuous vasopressin infusions have been used in severely symptomatic neurocritically ill patients and also those requiring rapid and tight control of serum sodium concentrations and urine output. Most patients achieve a goal UOP of < 100 mL with infusion rates of 0.5 to 3 μUnits/kg/hr[31,34] (Table 10).

In addition to vasopressin or DDAVP, patients who are hypernatremic secondary to DI should receive fluid replacement therapy. The amount of fluid to replete can be calculated by determining the patient's free water deficit: 0.6 X (weight in kg) X (1-140/measured plasma sodium in mEq/L). Alternatively, free water can be replaced in a 1:1 ratio with urine output every 1 to 2 hours until DDAVP or vasopressin is appropriately titrated. Free water replacement can be accomplished with intravenous infusions of isotonic glucose solutions such as D5W.

Depending on the patient's condition, 0.45% saline may be the fluid of choice when lowering the serum sodium too quickly could result in detrimental effects such as in patients with cerebral oedema. In general, lowering serum sodium levels more quickly than 10 to 20 mEq/day may lead to adverse effects[28].

Furthermore, patients who are conscious may be prescribed water intake by mouth with close intake/output observation. Once out of the acute phase of treatment, parenteral forms of DDAVP should be converted to an oral or intranasal formulation, and vasopressin infusions should be converted to DDAVP. An equivalent dosing chart for conversions between desmopressin and vasopressin in various dosage forms has been provided in table 10[30].

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Table 7: Pharmacological treatment of CSW[1,2,3].

Drug	Mechanism	Duration of Therapy	Dosing	Adverse Effects	Monitoring	Comments
Fludrocortisone	Increase sodium reabsorption at the distal tubules	Until sodium and fluid balance stable; usually 5-7 days	0.1 to 0.2 mg PO BID or TID (Rhaman 2009)	Pulmonary edema, hypertension, hypokalemia	Serum sodium Volume status, serum glucose, serum potassium, blood pressure	-Usual onset of action is 3 to 5 days
Sodium chloride tablets	Replenish sodium	Until sodium and fluid balance restored; recommend to reduce dose by 3g/day to titrate off	1 g PO TID to start. May titrate daily by 3g/day to effect	Hypernatremia (rare)	Serum sodium	-Consider transition to hypertonic saline if effect is not achieved with less than 6g/day
0.9% sodium chloride	Replenish sodium and volume	Until euvolemia has been established	Dosing is patient-specific. May replace UOP hour-by-hour	Hyperchloremic metabolic acidosis, volume overload	Volume status Serum pH Serum Bicarbonate	
Hypertonic Saline (1.5-23.4 % sodium chloride)	Increases sodium concentration. May be used to induce a hyperosmolar state	Until sodium and fluid balance restored; recommend to titrate off	50-150 mL/hr Or 2 mL/kg bolus dosing until Na has increased by 5 mEq/L with resolution of symptoms	Hyperchloremic metabolic acidosis, phlebitis, extravasation, hypokalemia, hypocalcemia, volume overload	Serum sodium, serum potassium, calcium, chloride, bicarbonate	-Central line administration required for 23.4% saline (bolus only) and 3% saline at rates > 30 mL/hr -1.5% does not require central line; -Abrupt discontinuation can result in rebound hyponatremia

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2. Rahman M, Friedman WA. Hyponatremia in neurosurgical patients: clinical guidelines development. Neurosurgery. 2009;65(5):925-35; discussion 35-6.
3. Yee AH, Burns JD, Wijdicks EF. Cerebral salt wasting: pathophysiology, diagnosis, and treatment. Neurosurg Clin N Am. 2010;21(2):339-52.

Conclusion

Disorders of sodium and water homeostasis are common in critically ill neurologic patients. Proper management necessitates an accurate diagnosis of the type of dysnatremia. Unfortunately accurately diagnosing dysnatremias is often difficult since specific diagnostic criteria are lacking for certain dysnatremias and additional comorbidities cloud interpretation of clinical symptoms.

Prudent selection of therapeutic strategies and diligent monitoring are important steps to preventing potentially fatal consequences as a result of contrasting treatment strategies for the various types of sodium disorders.

A keen understanding of the pharmacotherapy used to treat these disorders is critical to the management of these patients.

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Table 8: Etiology of Central Diabetes Insipidus[1,2].

Primary	· Genetic (5% of cases) o Autosomal dominant/recessive (AVP)-neurophysin gene defects o X-linked recessive and DIDMOAD syndrome · Congenital malformations · Idiopathic (up to 50% of cases)
Secondary	· Trauma o Neurosurgery and head injury · Neoplastic o Germinoma o Meningioma o Craniopharyngioma o Pituitary adenoma with suprasellar extension o CNS lymphoma o Leukemia and metastatic o Surgical removal of pituitary neoplasm · Vascular o Aberrant inferior hypophyseal arterial system o Internal carotid aneurysm · Inflammatory o Granulomatous disease § Neurosarcoidosis § Wegener's disease § Langerhan's histiocytosis o Autoimmune § Lymphocytic neurohypophysitis · Infections o Meningitis o Viral encephalitis o Toxoplasmosis o Tuberculosis · Toxins · Hypoxic/ischemic

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Critical review

Table 9: DDAVP in Treatment of Central DI[1,2,3,4].

Formulation	Dose	Indication	Onset	Duration	Advantages	Disadvantages
DDVAP, SQ	1 mcg SQ PRN	Acute treatment	1-2 hrs	8- 16 hrs	Immediate bioavailability	Requires frequent monitoring, injection site reaction
DDVAP, Intranasal	1 spray (10 mcg) QHS to BID	Maintenance treatment	40-55 min	6-18 hrs	Ease of administration, less frequent dosing	Fixed dose, require refrigeration
DDVAP, Oral Tablets	0.1-0.3 mg PO BID-TID	Maintenance treatment	40-55 min	6-18 hrs	Ease of administration, less side effects	Frequent administrations, larger doses to achieve effects

Abbreviations: SQ, subcutaneous; QHS, nightly; BID, twice a day; TID, three times a day; PO, daily

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Table 10: Vasopressin analogue dosing in Central DI[1,2].

Medication	IV	Continuous IV infusion	SQ	IM	PO	Intranasal
Vasopressin (Pitressin®)	5-10 units	0.5-1 units/hr	5-10	5-10	n/a	n/a
Desmopressin (DDAVP®)	1-2 µg	n/a	1-2 µg	n/a	0.1-0.6 µg/day	10-40 µg/day

Abbreviations: IV, intravenous; SQ, subcutaneous; IM, intramuscular; PO, per oral.

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