SAS Journal of Surgery ISSN 2454-5104
SAS J. Surg., Volume-3; Issue-5 (May, 2017); p-118-121
Available online at http://sassociety.com/sasjs/

Review Article

Hyponatremia: A Review

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Abstract: Syndrome of inappropriate antidiuretic hormone secretion is a clinical syndrome which enhance the secretion or action of ADH (antidiuretic hormone),which causes the body to retain water and certain levels of electrolytes in the blood to fall (such as sodium) .It is the most common cause of hyponatremia seen in hospitalized patients. It has various etiologies like malignancy, pulmonary diseases, CNS diseases and some medications. Symptoms of SIADH depend on the degree of hyponatremia and the rate at which it develops. Serum sodium below 120mmol/L can cause life-threatening symptoms, while gradual decline causes nonspecific symptoms. Vasopressin-receptor antagonists (vaptans) would provide a more effective method to treat hyponatraemia secondary to SIADH. The review focuses on syndrome of inappropriate antidiuretic hormone secretion as a cause of Hyponatremia and management of it which may help in the prevention of Hyponatremia.
Keywords: syndrome of inappropriate antidiuretic hormone secretion (SIADH), hyponatremia.

INTRODUCTION

Hyponatremia is defined as a decrease in the serum sodium concentration (<135mmol/L), is the most common electrolyte disturbance encountered in clinical practice. It is seen in 15–28% of hospitalized patients especially the geriatric population [1, 2]. Many hyponatremic cases are mild and asymptomatic but in severe cases show several neurological symptoms and even death may occur. Hyponatremia and it treatment can either directly or indirectly cause substantial morbidity and mortality. Mortality rate is higher in severe hyponatremic patients with wide range of underlying diseases and also the risk increases due to overly rapid correction.

Mainly hyponatremia is caused by either dilution of the serum sodium concentration or by the excessive sodium/potassium losses in excess of water. However majority of hyponatremia cases are due to excess water retention by the kidney as result of arginine vasopressin secretion.

Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

SIADH is a clinical syndrome, which enhance the secretion or action of ADH (antidiuretic hormone). It is the most frequent cause of hyponatremia; this condition was first described in patients with bronchogenic carcinoma in whom a physiologic stimulus for release of the antidiuretic hormone was lacking, by Bartter and Schwartz [3]. In a healthy body, arginine vasopressin (AVP) or antidiuretic hormone (ADH) is secreted from the posterior lobe of the pituitary gland in response to a decrease in plasma volume or an increase in serum osmolality to retain the water. A patient with SIADH; arginine vasopressin was independent of plasma osmolality and have unregulated secretion of vasopressin cause hypo tonicity of the serum. As a result of high concentration of vasopressin combined with water intake leads to antidiuresis finally resulting in hyponatremia.

Causes of SIADH

In SIADH the increased secretion of ADH by the posterior pituitary gland is due to various conditions like malignancy, pulmonary disorders, CNS disorders and some medication these are summarized in Table-1.

SIADH is common in malignant patients associated with ectopic secretion ADH, especially with small cell carcinoma of the lung [4]. In addition many drugs can stimulate the stimulation AVP secretion or enhance its action (SSRIs, TCAs). It has been estimated that 12% of the hospitalized patients on SSRI therapy develop SIADH and the drug 3, 4- Methylene dioxymethamphetamine which is an illegal recreational drug cause SIADH induced hyponatraemia [5]. Many central nervous system (CNS) disorders like stroke, brain tumor, infective disorders, trauma and hemorrhage can enhance the ADH release are associated with SIADH. 70% of the patients with subarachnoid hemorrhage may develop hyponatraemia

due to SIADH [6]. It also commonly occurs after surgery (postoperative states) in patients who undergo major abdominal and thoracic surgical procedures as well as chronic pain syndromes can result in increased secretion of ADH. SIADH is one of the most frequent causes of hospitalized patients with AIDS, which is related to adrenal insufficiency [7].

Table 1: Causes of SIADH

Malignant diseases	**Pulmonary Disorders**	**Drugs**	**CNS Disorders**	**Miscellaneous**
Small cell lung cancer Neck cancer Mesothelioma GI tract malignancy Pancreatic malignancy GU tract malignancy Lymphoma Sarcoma	Pneumonia(bacterial, viral) Tuberculosis Abscess Aspergillosis Positive pressureventilation	Selective serotonin reuptake inhibitors Tricyclic antidepressants Phenothiazines Haloperidol Carbamazepine Desmopressin Prostaglandins 3,4-Methylene dioxymethamphetamine Quinolones Leveteiracetam Cyclophosphamide Vincristine NSAIDS	Meningitis Encephalitis Subarachnoid haemorrhage Subdural haemorrhage Traumatic brain injury Brain tumors Multiple sclerosis Guillain–Barre syndrome Acute intermittent porphyria	HIV Hereditary Pain Idiopathic postoperative

Clinical features

The symptoms of SIADH depend on the degree of hyponatremia, the rate at which hyponatremia develops and osmotic gradient between intracellular and extracellular fluids. Patients who having mild Hyponatremia (>130 mmol/l) which decreases slowly over a long period of time may be completely asymptomatic [8]. Patients, with serum sodium concentration in between125 and130 mmol/l there can be nonspecific symptoms such as anorexia, vomiting, nausea, irritability, headaches, lethargy and muscle cramps. Patients who have undergone rapid declines in sodium concentration tend to have more symptoms. A serum sodium concentration less than 120 mmol/l is considered serious, irrespective of the rate of decline. With this degree of hyponatremia, patients can experience cerebral edema, which may cause headache, nausea, restlessness, irritability, muscle cramps, lethargy, hyporeflexia, confusion, coma, or seizures and also can cause permanent brain damage and even death [9].

Diagnosis of SIADH

The diagnosis of SIADH should carried out carefully; since it has various etiologies .A complete medical history including co morbidities ,current medication, patients symptoms and physical examination are essential .There are no significant findings in the physical examination of a patient with SIADH, although signs of dehydration or edema would make the diagnosis unlikely. Patients with moderate to severe hyponatremia need to be thoroughly assessed to find out potential complications.

The key points in diagnosing SIADH are the serum sodium concentration, urine sodium concentration, tonicity of plasma and urine and clinical volume status.

Diagnostic criteria for the diagnosis of SIADH

1. plasma osmolality<280 mosmol/kg, or
1. Plasma sodium concentration <135 mmol/l
2. Inappropriate urinary concentration (Uosm>100 mosmol/kg) for hyponatraemia
3. Patient is clinically euvolaemic
4. Elevated urinary sodium (>40 mmol/l), with normal dietary salt and water intake
5. Exclusion of hypothyroidism, diuretics therapy and glucocorticoid deficiency

SIADH as a diagnosis of exclusion, it is important to rule out thyroid, liver, cardiac, adrenal and kidney dysfunction through laboratory testing likes thyroid-stimulating hormone level, cortisol stimulation test, brain natriuretic peptide level, liver function tests, serum blood urea nitrogen level, and serum creatinine level) [9, 10]. Hypouricemia may be caused as a result of increased excretion of nitrogen waste and plasma dilution.

Management of SIADH

Accurate diagnosis of SIADH and the differentiation from other causes of hyponatremia is the first essential step in determining appropriate treatment. The treatment of SIADH is largely based on expert opinion and uses agents commonly approved for indications other than for hyponatremia [11]. These treatment agents include fluid restriction, demeclocycline, lithium, loop diuretics in combination

with salt tablets, urea tablets and hypertonic saline (3% NaCl). Fortunately, this situation has recently improved with vasopressin receptor antagonists, also known as vaptans.

Fluid restriction

Fluid restriction is the first line treatment of SIADH-induced mild hyponatremia not requiring urgent intervention. It is about 800 – 1200 ml per day is generally advised, according to severity of hyponatraemia. Fluid restriction causes a negative fluid balance that will increase the serum sodium concentration but it not enough to manage symptomatic hyponatraemia.

Demeclocycline

Demeclocycline is a tetracycline derivative, which is used in the treatment of SIADH. The recommended dosage for SIADH is 600–900 mg/day. It cause nephrogenic diabe¬tes insipidus, this effect has been used to treat the hyponatremia of SIADH [12].

Lithium

Lithium carbonate, an antidepressant drug also causes nephrogenic diabetes insipidus and this property of lithium has been used to treat SIADH. The efficacy of lithium is unpredictable as not all patients develop nephrogenic diabetes insipidus and it not consider as long term treatment for SIADH. Nephrogenic diabetes insipidus is not always reversible, with chronic treatment sometimes producing interstitial nephritis and end-stage renal failure [13].

Saline infusion

Intravenous infusion of hypertonic saline (3% and 5%) mainly used for the correction of severe hyponatraemia, with serious or life threatening neurological complication as it rapidly raise the serum sodium. For patients with severe neurological symptoms, an IV bolus of 100ml 3% saline can be administered.

Plasma sodium concentration will rise in some patients with SIADH who are treated with intravenous normal (0.9%) saline, particularly if urine osmolality is less than >530mOSm/kg. However this normal saline is used for patients in whom the differentiation between hypovolaemia and euvolaemia is difficult; in this situation, intravenous saline is a safer first line treatment than fluid restriction because fluid restriction may exacerbate hypovolaemic hyponatraemia.

Urea

Urea has been used to correct hyponatremia in SIADH because it cause osmotic diuresis and enhanced water excretion in dosages of 10–40 g/day.

Loop diuretics

Loop diuretics can be used to treat SIADH because it induces a water diuresis. Furosemide may be given orally or intra¬venously in a dosage as high as 10–40 mg/h, with or without replacement of any sodium lost by infusions of 3% saline. These regimens have been used successfully to treat SIADH.

Vasopressin receptor antagonists (vaptans)

The recent introduction of renal vasopressin receptor antagonists (conivaptan, tolvaptan) represents a new efficient management of SIADH. These are the first agents approved specifically for the treatment of SIADH. Vaptans work by preventing the antidiuresis caused by circulating vasopressin and cause removal of water from the body without loss of electrolytes results in an increase in serum [Na+].Tolvaptan which is available in oral form is indicated for patients with clinically significant euvolemic or hypervolemic hyponatremia (serum sodium <125 mmol/L) and also for mild hyponatremia (serum sodium<125–135 mmol/L) in symptomatic patients, including patients with heart failure and SIADH that has resisted conventional therapy . The recommended dosage for SIADH is 15–30 mg/day.Conivaptan is available as intravenous parenteral preparation for euvolemic hyponatremia caused by SIADH .An initial loading dose of 20 mg over 30 min is recommended and followed by a continuous infusion at a rate of 20 mg/day for up to 4 days [14].

CONCLUSION

In this present scenario, Hyponatraemia is the commonest electrolyte abnormality and SIADH is the most frequent underlying pathophysiology. An accurate diagnosis is essential for the treatment of SIADH so must consider patient's co morbidities, medication, and symptoms. As a diagnosis of exclusion, appropriate tests must be done to find out other potential causes of hyponatremia. The introduction of the vasopressin-2 receptor antagonists has allowed clinicians specifically target the underlying pathophysiology of SIADH .Early diagnosis and appropriate treatment will prevent serious complications of this common disorder.

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