WHAT IS ANTIDIURETIC HORMONE?
Antidiuretic hormone (ADH), also called vasopressin for its pressor effect, is a regulatory hormone secreted by the posterior pituitary in response to increased serum osmolality. ADH is actually synthesized in the hypothalamus, mostly in the supraoptic nuclei, though one-sixth can be synthesized by the paraventricular nuclei. ADH is then transported down the hypothalamic-hypophysial tract and is stored in large granules in the nerve endings of the posterior pituitary (Neurohypophysis). ADH is released when nerve impulses from the supraoptic and paraventricular nuclei are stimulated by osmotic changes in the plasma. Release is immediate from the nerve endings by exocytosis and is then absorbed into the adjacent capillaries (1).

ADH, a polypeptide consisting of nine amino acids, is structurally similar to oxytocin and for this reason has some cross biological activity, including contraction of smooth muscles of the uterus, as well as the gastrointestinal tract. As can be seen in Figure 1, the amino acids phenylalanine and arginine are replaced with isoleucine and leucine in oxytocin (1).

<table>
<thead>
<tr>
<th></th>
<th>Amino Acid Sequence of antidiuretic hormone and oxytocin</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH:</td>
<td>Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-GlyNH2</td>
</tr>
<tr>
<td>Oxytocin:</td>
<td>Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-GlyNH2</td>
</tr>
</tbody>
</table>

ADH is excreted in response to the increase in osmolality of the plasma due to water loss and increasing sodium concentration. Sodium is the main contributor of the osmolality of plasma; therefore, sodium excretion, retention and cellular shifts can have a large effect on plasma osmolality. ADH causes an increased permeability of the collecting ducts and distal tubules to water and leads to an increase in resorption of water by the nephron. The half life of ADH is 15 to 20 minutes and its effects can be turned on and off rapidly in response to osmoregulators near the hypothalamus. Osmoreceptors are modified neuron receptors that, with an increase in plasma concentration, have fluid pulled out of the osmoreceptor cell, decreasing the size of the cell initiating a response in the hypothalamus to secrete more ADH. When the plasma is too dilute the opposite happens and ADH secretion is decreased. The exact location of these osmoreceptors is unknown but they are either the supraoptic nuclei themselves or located in the organum vasculosum in the anteroventral wall of the third ventricle (1). See Figure 2.
The mechanism by which ADH causes increased water resorption is by binding to V2 receptors on the collecting ducts cells and initiating formation of cAMP inside the tubular cell cytoplasm. This causes phosphorylation of elements in the special vesicles that have high water permeable pores called aquaporin-2 water channels. This causes translocation of the aquaporin-2-containing vesicles from their cystolic location to the apical membrane of the collecting duct (2). This allows water to diffuse into the peritubular fluid and then absorption to occur in the collecting tubules and ducts by osmosis. This process takes five to ten minutes and can be reversed in the same amount of time (1).

WATER AND SODIUM HOMEOSTASIS

Water:
Water is the largest constituent of the body representing 45-75% of total body weight depending on the amount of body fat. Water is in two major compartments: the Intracellular Fluid (ICF) which is about 30-40% of body weight and the Extracellular Fluid (ECF) which consists of the plasma, interstitial fluid and the lymph. The ECF constitutes about 22% of body weight.

Water leaves the body through the kidneys, lungs, skin and the gastrointestinal tract. Average water loss per day is 1500ml through the kidney and about 1000ml through the skin and the lungs. Gastrointestinal tract losses are usually very small. The kidney water loss is controlled by solute load and the level of ADH. An increase in solute load, as might occur with an increase in serum glucose in diabetes mellitus, causes an increase in water loss. On the other hand, ADH
controls the reabsorption of water in the distal tubules, leaving a more concentrated urine (3).

Sodium:
The principal cation of the ECF is sodium. Sodium is important in fluid balance. Changes in the concentration of sodium stimulates or turns off the secretion of ADH from the pituitary. Plasma is 93% water and 7% plasma proteins and lipids. Sodium ion is dissolved in plasma water. A normal plasma concentration of sodium is 136-145 mEq/L. There is only a small quantity of sodium in the cells. The bone can contain up to 1500mEq of sodium but only one-third is available for exchange. Most ingested sodium is excreted in the urine. The average diet meets normal sodium requirements, since it contains 100 mEq of sodium. The minimum daily requirement of sodium is about 15 mEq but the average diet can get up to 6-15 grams of sodium a day (260-650 mEq of sodium)(3).

Sodium excretion can occur from the skin but the major regulator of sodium is the kidney. The kidney under normal circumstance tries to excrete the same amount of sodium that is taken in. If the body needs to conserve sodium, the kidney is capable of excreting an almost sodium free urine. Sodium balance is influenced by aldosterone, which inhibits renal sodium excretion. Sodium is also effected by ADH which promotes water resorption and effects sodium concentrations (3).

<table>
<thead>
<tr>
<th>Table 1: Sodium conversion figures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mEq of sodium weighs 23 mg</td>
</tr>
<tr>
<td>Normal sodium plasma concentration is 136-145mEq/L</td>
</tr>
</tbody>
</table>

WHAT IS SIADH?

Syndrome of inappropriate antidiuretic hormone (SIADH) is a condition of dilutional hyponatremia in a euvolemic patient. SIADH is diagnosed if there is hyponatremia, hypo-osmolality of the serum, persistent renal excretion of sodium during the development of water retention, euvolemic fluid state and an inappropriate increase in urine osmolality (4). This condition can be acute or chronic and the approach to treatment is different for both. This condition of impaired water excretion is due to elevated levels of ADH, loss of osmoregulation or a lower set point for osmoregulation and will result in hyponatremia. Usually, this requires the administration of water as well, since high levels of ADH alone do not usually produce a lower sodium concentration (5). The condition of hyponatremia can be further aggravated by the production of atrial natriuretic hormone, suppression of plasma renin activity and the compensatory increase in urinary sodium excretion caused by the expansion of extracellular volume (5).
The decrease in plasma osmolality causes an increase in ICF. The regulatory response to the osmotic gradient is to move water into the cells or to shift solute out of the cells. This can potentially lead to cerebral edema or brain cell swelling. Since the movement of water is passive and solute shift requires active transport via the Na+K+-ATPase pump, water movement occurs more rapidly. Adaptive mechanisms in chronic SIADH are designed to protect the cell volume and minimize the effects of the cerebral edema and its symptoms. The movement of osmotically active substances, such as sodium, chloride, potassium, glutamate, taurine, myo-inositol and glutamine from inside the cells contributes to the adaptive response in chronic hyponatremia. These adaptive processes can take hours to days to occur. This is why the treatment of chronic SIADH is different than acute SIADH. Patients who have developed this adaptive mechanism can incur CNS injury and demyelination if corrected too rapidly (1,2,5).

ETIOLOGY OF SIADH
There are many causes of SIADH. These include ADH-secreting neoplasms, non-neoplastic lung disease, CNS disorders, AIDS, pain, nausea, major surgery and pharmacologic agents. Pain and nausea are physiologic stimuli for ADH secretion. This would be inappropriate in the absence of hypovolemia or hyperosmolality (5).

DIAGNOSIS OF SIADH
Hyponatremia in SIADH is not a disease but a manifestation of the disorder. By obtaining an accurate history, physical examination and appropriate laboratory data, the differential diagnosis for the hyponatremia may be developed. The use of four laboratory tests may help with the diagnosis: plasma osmolality; urine osmolality; the urine sodium concentration; and urine potassium concentration (5).

Patients with SIADH usually have a decreased plasma osmolality (<280mOsm/kg), decreased serum sodium (<130 mEq/L), increased urine osmolality (>100mOsm/kg) and an increased urine sodium of >40mEq/L. These findings in conjunction with normal adrenal and thyroid function as well as normal serum potassium and acid/base balance can be diagnostic of SIADH (5,6).

Patients with hyponatremia due to SIADH may be asymptomatic initially but demonstrate increasing signs and symptoms with decreasing sodium levels. The rate of development of hyponatremia may also influence onset of symptoms. Symptoms can be mild at first with nausea and malaise. As symptoms progress there is more central nervous system involvement, including anorexia, depression,
irritability, headache, lethargy, confusion and obtundation. When sodium levels are < 120mEq/ L or if the concentration is dropping rapidly, stupor, seizures and coma may present. With sodium concentrations of less than 110 mEq/ L patients may have extensor plantar responses, areflexia and pseudobulbar palsy (5). Many of the symptoms are similar to other conditions and to the process of aging and may be overlooked unless matched with the appropriate laboratory information.

**DRUG-INDUCED SIADH**

Drugs can be a common cause of electrolyte disturbances, one of which is hyponatremia. Drugs can cause hyponatremia by direct or indirect stimulation of ADH release from the posterior pituitary, although the exact mechanism is not known in many cases. Hyponatremia can also be caused by increased excretion of sodium, such as with thiazide diuretics.

### DRUGS COMMONLY CAUSING SIADH

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasopressin &amp; analogues</td>
<td>Vasopressin, desmopressin, oxytocin</td>
</tr>
<tr>
<td>Chemotherapeutic agents</td>
<td>vincristine, vinblastine, cisplatin,</td>
</tr>
<tr>
<td></td>
<td>cyclophosphamide, mephalan, vinorelbine,</td>
</tr>
<tr>
<td></td>
<td>ifosfamide, levamisole</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Fluoxetine, tricyclic antidepressants</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Hypoglycemics</td>
<td>Chlorpropamide, tolbutamide, glyburide</td>
</tr>
<tr>
<td>Others</td>
<td>Thiazides, ace-inhibitors, bromocriptine,</td>
</tr>
<tr>
<td></td>
<td>amantadine, carbidopa-levodopa, nicotine,</td>
</tr>
<tr>
<td></td>
<td>narcotics, nonsteroidal anti-inflammatory drugs, somatostatin</td>
</tr>
</tbody>
</table>

(Adapted from information in Belton, K. et al., Chan, T.Y.K., and Spigset, O. et al.)

**VASOPRESSIN AND ANALOGUES**

These agents can cause SIADH since they may cause water intoxication and dilutional hyponatremia. Desmopressin is used in children for nocturnal enuresis. If the child has greater than 250ml of fluid prior to his nightly dose, symptoms of water intoxication such as seizure can occur (7). This medication may also be given with imipramine which may augment the antidiuretic effect of the desmopressin (7). Desmopressin can also cause SIADH when used for bleeding abnormalities (7). The incidence is rare in patients with variceal bleeding with cirrhosis, since they have elevated levels of ADH which may have down regulated the V2 receptor and caused a resistance (7).
Oxytocin, if given in a large volume hypotonic solution for a prolonged period of time, can cause hyponatremia. The risk can be reduced by administering oxytocin in normal saline. Nasal administration of oxytocin in excessive doses can also cause SIADH (7).

ANTINEOPLASTIC AGENTS
When suspecting an antineoplastic agent as the cause for SIADH, one must remember that many neoplasm’s themselves can cause an ectopic production of ADH. These include small cell lung cancer (15%), head and neck cancers (3%) and non small cell lung cancers (<1%). SIADH can also occur with primary brain tumors, hematological malignancy, melanoma, sarcoma, gynecological cancers, gastrointestinal cancers, breast, prostate or bladder cancers (5).

Vincristine causes hyponatremia by a suspected neurotoxic effect on the cells which release ADH. It is a commonly used agent for leukemia, lymphoma and other solid tumors. Overdose of vincristine will also cause hyponatremia. The other vinca alkaloid, vinblastine is less likely to cause hyponatremia and also appears less neurotoxic (7). SIADH has been reported in less than 1% of the patients using vinorelbine, a semi-synthetic vinca alkaloid (8).

Cyclophosphamide and ifosfamide are structurally related and cause SIADH and hyponatremia. The effect appears to be transient and is related to the metabolites that mediate an increase in release or effect of ADH. This is usually seen with high dose therapy though there are reported cases with low doses of cyclophosphamide. The importance of the antidiuretic effect of antineoplastic agents is important since many patients will require fluid loading to prevent uric acid accumulation and cyclophosphamide induced cystitis (7).

Other antineoplastics such as melphalan, interferon alpha and gamma and cisplatin can also induce ADH secretion and a secondary hyponatremia. A case report of levamisole-induced SIADH is reported in the NEJM. A 64-year-old male was treated with 5-FU and levamisole orally for colon carcinoma with a drop in sodium level to 115mMol/ L with symptoms requiring three days of hypertonic saline. As there were no reports of this reaction in the literature, he was re-challenged and again developed hyponatremia, though monitored and treated prior to being below 133mMol/ L (9).

ANTIDEPRESSANTS
Tricyclic antidepressants (TCA), monoamine oxidase inhibitors and selective serotonin receptor inhibitors (SSRI) have all been implicated in causing hyponatremia. Most of these patients had in common advanced age with a mean
age of 58 years for patients on TCA's and 75 years for SSRI's and concomitant drug therapy with an agent that can cause hyponatremia, including thiazide diuretics and chlorpropamide. The risk of hyponatremia was highest in the first few weeks of therapy. The mechanism for this is believed to be due to increased thirst (10). A case report in the Journal of American Geriatric Society reinforces the fact that fluoxetine, an SSRI, can cause SIADH in the elderly as reported in an 84-year-old patient, with a serum sodium of 105 mEq/L and an serum osmolality of 235 mOsm/kg compared to 590 mOsm/kg in the urine. The patient's symptoms were weakness, nausea and mental deterioration after receiving fluoxetine 40 mg daily for two weeks (11).

ANTIPSYCHOTICS
Patients with psychological disorders have an increased occurrence of psychogenic polydipsia, transient increases in ADH during a psychotic exacerbation (12), increased thirst due to the anticholinergic effects of the medication and are at risk for drug interactions that can cause hyponatremia and SIADH. Phenothiazines, including chlorpromazine, fluphenazine, trifluoperazine and thioridazine, as well as haloperidol, thiothixene and clozapine have been reported to cause hyponatremia (10,13). The mechanism by which these drug causes SIADH is unknown, but may be related to increased thirst or increased release of ADH leading to water intoxication (7).

In 1979, Peck and colleagues reported a case of haloperidol-induced SIADH in Clinical Pharmacology and Therapeutics. They described a 54-year-old male with chronic schizophrenia who developed SIADH, while receiving haloperidol, with a serum sodium of 111mEq/L, serum osmolality of 225 mOsm/L and urine osmolality of 325 mOsm/L. Haloperidol was discontinued and later the patient was re-challenged with similar laboratory results and symptoms. In this patient they documented the patient's inability to excrete a water load while on haloperidol and his ability to excrete water load off haloperidol (13). Other case reports have documented similar results with other antipsychotics (7).

NEUROLEPTICS
Carbamazepine causes an increased release of ADH and an increased response to ADH in the tubules. This side effect is actually used to treat Diabetes Insipidus. The occurrence of SIADH due to carbamazepine is higher in patients greater than 39 years of age and in patients with higher carbamazepine serum levels. Other risk factors include concomitant thiazide use, psychogenic polydipsia or low serum sodium levels at start of therapy. It is now believed that this effect can occur at lower doses (200mg BID) and soon after initiation of therapy (three days) (7), though earlier reports indicate doses of 600-2000mg/ day were necessary for one to three months (10).
HYPOGLYCEMIC AGENTS
Sulfonylureas, mainly chlorpropamide, have been reported to cause SIADH at normal doses by increasing secretion of ADH or increasing the renal effect of ADH. Advanced age and concomitant diuretic or ace-inhibitor use were risk factors for the development of SIADH. Chlorpropamide caused SIADH in 7 to 10% of study populations and because of this in controlled conditions it is used to prevent free water clearance in such diseases as diabetes insipidus and anterior pituitary insufficiency. Tolbutamide and glyburide treated patients only rarely developed SIADH (4.6% and 1.6% respectively)(7).

THIAZIDE DIURETICS
Whether the hyponatremia of thiazide diuretic use is truly SIADH is debatable. This hyponatremia is usually accompanied by hypokalemia, hypomagnesemia and alkalosis. The increase in ADH is appropriate for the volume contraction. Contributing factors to hyponatremia include a reduction in the renal excretion of free water induced by the drug, impairment of urinary dilution by blocking sodium reabsorption in the distal tubule and volume depletion. Potassium depletion may cause a compensatory shift of sodium into cells and magnesium may decrease the renal diluting ability (7). Excessive water intake and urinary sodium loss may also play a role.

Though the degree of hyponatremia is mild, the elderly and female population may be at increased risk. High doses of thiazide (50-100mg/ day) may be more problematic. The combination of a thiazide with a potassium-sparing diuretic, amiloride more commonly than triamterene, may have a greater tendency for hyponatremia, since this combination is more naturetic than thiazide alone. Combinations with other drugs, such as those discussed, may also increase the risk of hyponatremia (7).

Indapamide is a thiazide-like diuretic used in the treatment of hypertension and edema. Two case reports by Chan in The Annals of Pharmacotherapy in 1995 discusses the hyponatremia and hypokalemia seen following initiation of therapy with indapamide in two elderly women. He concluded that indapamide can cause symptomatic hyponatremia with concomitant electrolyte imbalances as seen with other thiazide diuretics and due to the same mechanisms as other thiazides (14).

ACE-INHIBITORS
Reports of hyponatremia due to ace-inhibitors, such as lisinopril, enalapril, ramipril and captopril, are rare and may be attributed to concomitant drug therapy with thiazide diuretics in many reports. In all cases the sodium concentration dropped when ace-inhibitors were started and normalized when discontinued. One case was proven with a water loading test and drug rechallenge
in which the patient received enalapril. The mechanism may be due to a
stimulation of thirst or ADH secretion (7).

OTHER DRUGS
Dopamine may increase ADH levels. Cases of SIADH have been reported with
the use of dopaminergic agents, such as bromocriptine, amantadine and
carbidopa/levodopa combinations. The mechanism for the increased ADH
levels is an increase in secretion (7).

Endogenous opioids are involved in the osmotic and non-osmotic release of
ADH. Morphine and methadone can cause an antidiuresis in hydrated animals
and humans (7).

There are increased levels of ADH in smokers following smoking and wearing a
transdermal patch. Nicotine has been found to decrease renal water excretion in
animals by increasing ADH release (7).

Nonsteroidal anti-inflammatory agents inhibit prostaglandin’s. Prostaglandins are
important in the modulatory effects of renal water metabolism causing an
impairment in the ability to maximally concentrate the urine. NSAID’s by
inhibiting prostaglandins augment the effects of ADH and impair free water
excretion. There are case reports for ibuprofen, diclofenac, indomethacin,
piroxicam and sulindac. Risk factors may include advanced age or conditions that
limit free water excretion (chronic renal failure, heart failure, or concurrent use of
thiazide diuretics, other analgesics or cyclophosphamide.) Hyponatremia has also
been reported in neonates given indomethacin for closure of patent ductus
arteriosus (7).

Somatostatin is a potent inhibitor of pituitary and pancreatic hormone release. It
is used in treatment of variceal bleeding, pancreatic, biliary and intestinal fistula
and endocrine tumors. Patients given high doses of somatostatin (250mcg bolus)
have increased levels of ADH and increased urinary osmolality, decreased free
water clearance and symptomatic hyponatremia (7).

PRIMARY PREVENTION

Primary prevention is important to consider when starting drug therapy. Patients
at increased risk of SIADH are the elderly and patients on multiple drug therapy.
Other patients at risk include those with a disease or cancer commonly associated
with SIADH, prior history of SIADH, postoperative state, especially in pre-
menopausal females or transsphenoidal hypophysectomy. Also, patients who are
at high risk should not be given hypotonic intravenous fluids, but rather normal
saline is the preferred fluid (15).
MANAGEMENT OF DRUG INDUCED SIADH

If the diagnosis of SIADH is suspected, the source of the imbalance must be determined. If many of the diseases which can cause SIADH are not obvious, a review of medications for possible drug induced disease is required. If a drug is highly suspected, it should be discontinued or switched to another agent with less chance of aggravating the hyponatremia. Management of the hyponatremia is required even if the cause of SIADH is found and treated (5,15).

A determination of the hyponatremia being acute (less than 48 hours) or chronic (greater than 48 hours) will determine how aggressively the hyponatremia is corrected as well as presenting symptoms. As discussed previously, in chronic disease there is an adaptive mechanism, which in the setting of too rapid of sodium correction will cause cerebral edema or demyelinating lesions (central pontine myelinolysis) and death.

Acute SIADH
Asymptomatic
In patients who present with SIADH with mild or no symptoms and a sodium concentration of greater than or equal to 125 mEq/L, less aggressive therapy is appropriate. Initiate a fluid restriction of 800 to 1000ml/24hours or to a volume less than the sum of insensible losses and urinary output (5,15). Normal saline can be used to correct any ECF contraction if present and will stop the osmotic release of ADH and allow free water to be excreted. The effect on plasma sodium may be small (5).

Symptomatic
If patients present with more severe symptoms and/ or rapidly developing hyponatremia, more aggressive sodium repletion may be necessary. Sodium levels of less than 105 mEq/L or symptomatic seizures or coma at higher serum sodium levels will require hypertonic saline (3% NaCl) at a rate sufficient to increase the sodium by 1-2 mEq/L per hour but by no more than 12 mEq during the first 24 hours or to greater than 125mEq/L. The administration of furosemide at 1mg/ kg will help promote diuresis in these patients. This may require more hypertonic saline to compensate for the naturesis caused by the furosemide. Patients should also be monitored for hypokalemia and hypomagnesemia. Once sodium levels are greater than 125mEq/L the fluid may be changed to normal saline. Once corrected, the patient should adhere to a strict fluid restriction, if predisposed to recurrence of SIADH (5,15).
Chronic SIADH
Asymptomatic
Water restriction as stated above may be enough to treat these patients in conjunction with discontinuation of the offending agent or correction of the underlying disease state. Do not raise the serum sodium by more than 0.5-1 mEq/ L per hour and no more than 10-12 mEq/ L in the first 24 hours. In some patients, SIADH may be chronic and resistant to all attempts at initial treatment and must be treated pharmacologically as discussed below (15).

Symptomatic
Patients with chronic, symptomatic SIADH may be corrected with hypertonic saline or normal saline if needed to raise the serum sodium to at least 125mEq/ L, but it must be done more slowly to prevent CNS demyelination. As discussed earlier the adaptive mechanisms of the brain have compensated for the decrease in osmolality and sodium and any rapid change may damage the cells (5,16). If the patient is symptomatic, the serum sodium can be corrected at a rate of no more than 0.5mEq/ L per hour. This can be achieved with normal saline and furosemide to promote diuresis of the fluid load. Correction beyond 125 mEq/ L during the initial treatment of chronic symptomatic SIADH is usually not necessary to stop symptoms and can be dangerous (7).

Risk of Too Rapid of Correction
The major concern in correcting serum sodium is the induction of cerebral pontine myelinolysis (CPM). This is a condition that can cause permanent brain damage or death. It is more common in patients with alcoholism, severe debilitation or malnutrition and patients with chronic SIADH (15). Other groups at increased risk include pre-menopausal women after surgery, elderly patients taking thiazide diuretic, patients with psychogenic polydipsia (2). The adaptive mechanism of the body to hyponatremia and hypoosmolality are design to protect the brain cells from swelling and causing cerebral edema and its symptoms (5,15).

Cerebral Pontine Myelinolysis is associated with too rapid an increase in serum sodium concentration in the first 24 hours of therapy. Patients in which the sodium is increased by more than 12 mEq/ L in the first 24 hours may develop this condition with risk of permanent damage (15). CPM is characterized by flaccid paralysis, dysarthria, bulbar weakness, abnormal eye movement, coma and dysphagia (5,15). It is suggested that over-correction of serum sodium can be treated with hypotonic fluids and desmopressin to prevent neurological sequelae (2).
Calculations for correcting sodium

\[(\text{[Na+] required} - \text{[Na+] actual}) \times \text{weight} \times 0.6 \text{ for males or 0.5 for females} = \text{quantity of sodium necessary to raise level by a desired amount}\]

Example:
A 70 kg male patient with a serum sodium of 115mEq/L, how many mEq will be required to increase his serum sodium to 125mEq/L?

\[(125-115) \times 70 \times 0.6 = 420 \text{ mEq of sodium}\]

3% NaCl (Hypertonic Saline) = 51.3 mEq of sodium/100ml
0.9% NaCl (Normal Saline) = 15.4 mEq of sodium/100ml

Divide the number of mEq's calculated to correct the serum sodium by sodium content of the correcting fluid to determine the number of milliliters to be infused. This volume is to be divided by the number of hours the correction is to occur to establish a final rate of infusion.

Example:
420 mEq divided by 15.4 mEq multiplied by 100ml = 2727ml of normal saline

If correcting over 24 hours, rate will be 113ml/hr.

When correcting serum sodium with hypertonic or normal saline, it is important to check serum sodium levels hourly (5). Stop the solution if you have corrected to the maximum daily allowable level and symptoms are controlled. The infusion can be stopped sooner if symptoms are controlled and the risk of cerebral pontine myelinolysis is high and more gradual increase in serum sodium can be accomplished with fluid restriction or other pharmacological therapy.

Pharmacological therapy of chronic SIADH

In many cases the cause of the SIADH is not found and underlying treatment of the manifestation of hyponatremia is necessary. Sometimes the drug therapy a patient is on cannot be stopped or changed and the underlying hyponatremia will need to be controlled pharmacologically and with fluid restriction (10).
Sodium Chloride tablets can be used to increase sodium levels. Since there is no defect in sodium homeostasis the increased sodium load might be expected to be excreted by the kidneys with only a small change in serum sodium. Some patients can be treated with a combination of sodium chloride and furosemide or even furosemide alone. Urea is used but requires the patient to have an intact thirst mechanism or they become at risk of developing a hypernatremic dehydration (10).

Demeclocycline is a tetracycline derivative with the ability to inhibit the renal effects of ADH. This agent is well tolerated, with the primary side effects being photosensitivity, nausea, gastrointestinal disturbances and nephrotoxicity. This agent can be tried in patients who are unresponsive to fluid restriction. The drug can be initiated at a dose of 150mg po QID and increased to 300mg po QID if necessary (10,17). A decrease in urine osmolality will begin in three to six days and polyuria may be evident in one to two weeks. After the initial response the dose can be lowered to the dose that keeps the serum sodium in normal range, which in many cases is 300-900mg per day. If a patient does not have an intact thirst mechanism, the polyuria may cause a severe hypernatremic dehydration. Since there have been reports of nephrotoxicity it is advisable to monitor serum creatinine and BUN for changes and discontinue therapy if they increase. The hypernatremic effect of demeclocycline slowly reverse with discontinuation of the drug. Photosensitivity can be prevented with sunblock and using caution when exposed to ultraviolet light (10,17). Although there are side effects and limitations, demeclocycline is considered the first line agent for treating chronic SIADH.

Lithium has been used for its effect in inhibiting the action of ADH and producing a reversible form of diabetes insipidus. Studies have shown that the initial response does not continue with prolonged therapy. Lithium also has central nervous system side effects such as confusion, disorientation, paresthesia and hyporeflexia. Lithium can also cause hypothyroidism, which causes a water retention and hyponatremia, and thyroid function tests need to monitored. Lithium will require monitoring of levels to prevent toxicity especially since there can be changing sodium and fluid levels in the treated patient. This agent is not considered a first line agent and should be tried only if other therapies have failed (10, 17).

Phenytoin inhibits the release of ADH from the pituitary. Its use is limited to patients with an endogenous excess of ADH. It is argued that phenytoin is useful in acute water intoxication and not chronic SIADH since it does not have a prolonged effect on hyponatremia. There are case reports of long term use of phenytoin for pituitary axis abnormalities but the drug needs to be monitored for signs of toxicity (17).
CONCLUSION
The syndrome of inappropriate antidiuretic hormone can be caused by a relative increase in ADH secretion, the kidney being more sensitive to the effects of ADH or the set point for the osmoregulatory system is lower allowing for a decreased level of serum osmolality to control ADH secretion. The diagnosis of this condition is based on a thorough history and physical exam of the patient with laboratory evaluation of electrolytes, plasma and urine osmolality. A knowledge of disease states and pharmaceuticals that can cause SIADH or hyponatremia is necessary to evaluate the treatment options for management of this disorder. Acute and chronic SIADH require different approaches to management to avoid central nervous system toxicity. Initial treatment of hyponatremia requires sodium repletion and may require furosemide to prevent exacerbation of CHF in some patients. Chronic SIADH can be treated with the pharmaceutical agents demeclocycline, the drug of choice for long term management in conjunction with fluid restriction. The consequence of not being aware of the signs and symptoms of hyponatremia and its management may be life threatening to the patient.

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