

## SYNDROME OF INAPPROPRIATE ADH SECRETION (SIADH)

### Pathophysiology

Antidiuretic hormone (ADH) is secreted by the posterior pituitary gland (neurohypophysis) and acts on the kidneys to induce water retention primarily at the level of the collecting ducts. SIADH results from inappropriate ADH secretion resulting in inappropriate retention of ingested/infused water. It is important to note that although water excretion is impaired, salt handling is NORMAL. i.e. The body attempts to get rid of the excess water by dumping sodium in the urine.

### Diagnosis

- clinically euvolemic (e.g. assess postural BP and pulse, JVP, mucus membranes and skin turgor)
- serum hypoosmolarity (serum osm  $<280$  mOsm/kg)
- hyponatremia (serum sodium  $<135$  mmol/L, but usually only investigate if  $<130$ ),
- urine sodium  $>20$  mmol/L
- urine osmolarity  $>$  serum osmolarity

The diagnosis of SIADH cannot be made if the patient is on diuretics or if renal, thyroid or adrenal function is abnormal

### Treatments

**\*\*\*CORRECT SLOWLY because of risk of central pontine myelinolysis\*\*\***

The maximum correction rate should be a rise of serum sodium no greater than  $0.5$  mEq/L/h or  $6-8$  mEq/L/day. In patients with severe symptoms, can increase the initial rate to  $1$  mEq/L/h for 2-3 hours and then decrease to above rate (especially if the drop in sodium was acute rather than chronic)

MONITOR serum lytes frequently to ensure that the serum sodium level is being corrected and that the rate of rise is less than  $8$  mmol/L/day. e.g. q6h initially then BID then OD

1) Treat underlying condition if possible

2) Fluid restriction

Inexpensive, takes several days to take effect, noninvasive, limited efficacy; only small daily increments in sodium, Effective for asymptomatic concentration achievable euvolemic hyponatremia, Compliance is difficult, therapy is uncomfortable for most patients, patients receiving certain IV therapies (antibiotics, chemotherapy, parenteral feeding) may be unable to have their fluid load restricted

3) Hypertonic saline 3% infusion

Rapid correction of Requires complex calculations hyponatremia of sodium requirements and the rate of replacement Effective in many cases of acute severe symptomatic or Requires laboratory monitoring chronic symptomatic and frequent

4) Conivaptan:

Conivaptan is for intravenous (IV) use only, Use large veins and change the infusion site every 24 hr

Begin with a loading dose of  $20$  mg IV administered over 30 min, Continue with  $20$  mg administered as continuous IV infusion over the next 24 hr for up to 4 days

#### Administration and Patient Monitoring

- Monitor serum  $[Na^+]$  and volume status frequently
- Limit rise in serum  $[Na^+]$  to  $<12$  mEq/L/ 24 hr and  $<18$  mEq/L in first 48 hr
- In patients whose serum  $[Na^+]$  rises undesirably rapidly (10-15% of patients), Conivaptan should be discontinued and serum  $[Na^+]$  and neurologic status carefully monitored; if serum  $[Na^+]$  continues to rise, Conivaptan should not be resumed
- The total duration of infusion of conivaptan (after the loading dose) should not exceed 4 days.
- Venous Access
- Administer Vaprisol through large veins and change the infusion site every 24 hr to minimize the risk of vascular irritation.
- Drug-Drug Interactions: P450 IIIA4 (\*\*\*) Important(\*\*\*)

#### Alternative Treatment Options:

- Water restriction-the primary therapy for hyponatremia in edematous states.
- Normal saline or increased dietary salt is given to patients with true volume depletion or adrenal insufficiency. The use of hypertonic saline is generally recommended only for patients with symptomatic hyponatremia.
- In SIADH since the urine osmolality is usually above 300mosm/kg, saline alone can worsen hyponatremia. Treatment options include fluid restriction, hypertonic saline and loop diuretics.

**Cost:**

<b>Product</b>	<b>Cost per vial/bag</b>	<b>Cost per 4 days of treatment</b>	
<b>3 % Saline 500ml</b>	<b>\$4.24</b>	<b>\$16.96</b>	
<b>Conviaptan 20mg vial</b>	<b>\$306.86</b>	<b>20mg \$1227.44</b>	<b>40mg dose \$2454.80</b>

**Conclusion:**

- There are no comparative trials with 3% saline.
- In placebo-controlled trials, approximately 9% of patients had too rapid of an increase in serum sodium that would put them at risk for osmotic demyelination.
- The half-life of the drug is between 6.87 and 8.7 hours. This could cause potential problems in anticipating the rate and rise in sodium levels
- There is a wide variability in elimination characteristics of the drug between patients.
- There are multiple potential drug interactions, since it is a potent P450 3A4 inhibitor, and sensitive substrate.
- No formal recommendations for renal or hepatic impairment dosing
- The medication is much more expensive than other treatment options
- There is no data supporting any better outcomes with this agent versus other treatment options  
There were >50% injection site reactions in patients receiving Conviaptan

**5) Demeclocycline**

150 to 300 mg po qid. Effective but very slow onset of action; requires, inexpensive, Not suitable for acute. Should be used for noninvasive symptomatic hyponatremia because of slow onset of action. Use requires caution in patients with renal or hepatic impairment, nephrotoxic, in some patients