GUIDELINES FOR THE ASSESSMENT AND MANAGEMENT OF HYPONATRAEMIA

Hyponatraemia is the most common electrolyte disturbance found in hospital inpatients. These guidelines provide an aide to managing this problem with specific emphasis on the **management of hypotonic hyponatraemia due to syndrome of inappropriate anti-diuretic hormone secretion (SIADH) and use of sodium chloride 1.8% (hypertonic saline) in acute and/or symptomatic hyponatraemia.**

List of abbreviations:

- ADH: Anti-diuretic hormone (also known as vasopressin or arginine vasopressin)
- SIADH: Syndrome of inappropriate anti-diuretic hormone secretion
- ACTH: Adrenocorticotrophic hormone
- CSWS: Cerebral salt wasting syndrome
- V2 receptor antagonists: Vasopressin 2 receptor antagonists
- SST: Short synacthen test
- SAH: Subarachnoid haemorrhage
- IPTR: Individual patient treatment request

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1. DEFINITION AND CLASSIFICATION OF HYPONATRAEMIA

Hyponatraemia is defined as a serum sodium concentration of < 135 mmol/L. It can be classified on the basis of biochemical severity, symptoms, speed of development and volume status.

1. Classification of hyponatraemia on the basis of the serum sodium concentration:

- Mild: 130-135 mmol/L
- Moderate: 125-129 mmol/L
- Profound: <125 mmol/L

2. Neurological symptoms due to hyponatraemia are a result of cerebral oedema and can be classified as 'moderately severe' and 'severe' (see table 1).

Table 1

Severity	**Symptoms**
Moderately severe	Nausea without vomiting, confusion, headache
Severe	Vomiting, cardio-respiratory distress, abnormal and deep somnolence, seizures, coma

3. While any biochemical level of hyponatraemia can result in cerebral oedema, the speed of development of hyponatraemia usually determines whether cerebral oedema, and therefore signs and symptoms requiring urgent treatment, develop.

   'Acute' hyponatraemia develops over a duration of less than 48 hours and 'chronic' hyponatraemia would have developed over a period greater than 48 hours.

   'Acute' hyponatraemia warrants urgent treatment to prevent the development of cerebral oedema. In contrast, a symptomatic patient with chronic hyponatraemia is more at risk from rapid correction of hyponatraemia with the risk of developing osmotic demyelination syndrome. Signs of osmotic demyelination develop 3-4 days after treatment and signs/consequences include dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death.

   - ❖ As a general rule, **target** for a 5 mmol/L rise in serum sodium concentration following any treatment (i.e. fluid restriction, hypertonic sodium chloride, demeclocycline, tolvaptan, oral sodium) but **limit** the increase in serum sodium concentration to 10 mmol/L in the first 24 hours of treatment and 8 mmol/L during every 24 hours thereafter, until a serum sodium level of 130 mmol/L is reached.
   - ❖ If sodium rises by more than 10 mmol/L in the first 24 hours or by more than 8 mmol/L during every 24 hours thereafter then corrective action to re-lower the sodium must be considered.

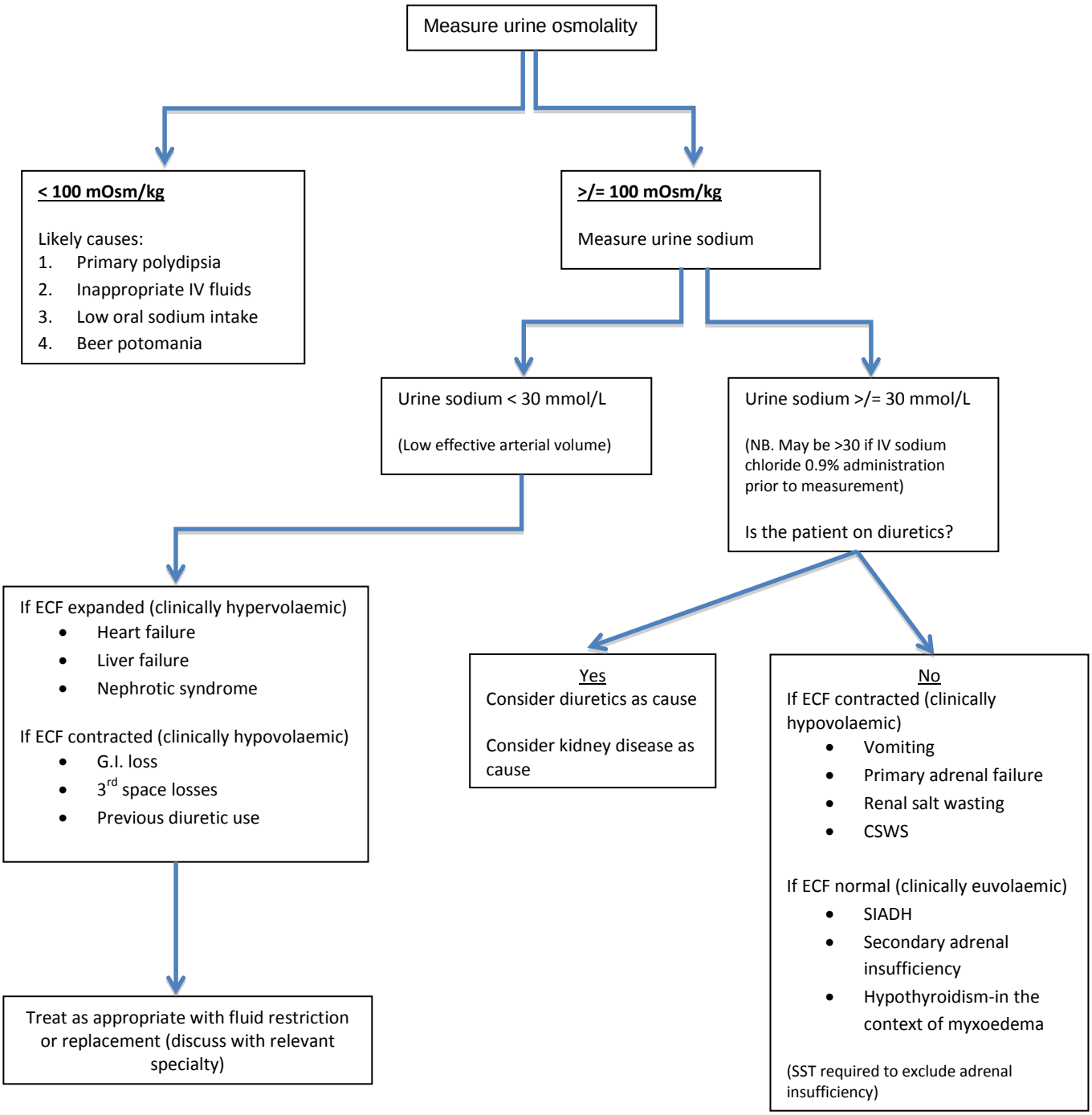
4. Patients' volume status is another way to classify and potentially determine the cause of hyponatraemia. However, in practice, clinical assessment of volume status is unreliable with a low sensitivity (0.49) and specificity (0.4). Nonetheless, blood pressure, heart rate and urea levels should be taken into account and can be used as a guide when determining the appropriate treatment for hyponatraemia. For example, hypertonic sodium chloride MUST NOT be used to resuscitate a hypovolaemic patient who is likely to be hyponatraemic due to volume depletion.

2. ASSESSMENT OF PATIENTS WITH HYPONATRAEMIA (Na < 135 mmol/L)

1. Measure plasma osmolality. Hypotonic hyponatraemia confirmed if plasma osmolality <275 mOsm/kg
2. If plasma osmolality >275 mOsm/kg, then look for causes of non-hypotonic hyponatraemia e.g., hyperglycaemia, ethanol or for pseudohyponatraemia due to paraproteinaemia or hypertriglyceridaemia and treat accordingly.

Are there neurological symptoms/changes (see table 1)? → If yes, consider treatment with hypertonic sodium chloride (see below for further guidance); send a urine aliquot to the lab requesting osmolality and sodium prior to treatment.

3. Investigate and determine cause of hypotonic hyponatraemia as follows (Figure 1):



3. MANAGEMENT OF SYMPTOMATIC AND ACUTE HYPONATRAEMIA

The approach to the **management of hyponatraemia is dependent on the rate of development of hyponatraemia AND/OR the presence of neurological symptoms.** It is often difficult to determine whether a patient's hyponatraemia is acute or chronic therefore unless there is good reason to believe that the hyponatraemia is acute (e.g. post-resection of the prostate, polydipsia, recent thiazide prescription, MDMA use, colonoscopy preparation, oxytocin, recent desmopressin or terlipressin therapy) it should be considered chronic and treated accordingly (i.e. find and treat underlying cause in the first instance).

Symptomatic (neurological symptoms) and acute hyponatraemia can be treated with hypertonic sodium chloride. However, there must be sufficient confidence that symptoms are due to hyponatraemia before administration of hypertonic sodium chloride. If hyponatraemia is biochemically 'mild' then only accept causality in exceptional cases.

Specialist (endocrine/renal) advice and/or review **must** be obtained before administration and prescription of hypertonic sodium chloride.

Correction of concurrent hypokalaemia if present will cause a rise in serum sodium concentration and this must be taken into account when using any specific treatment to correct hyponatraemia.

3.1. Fluid replacement in patients with Hypovolaemic Hyponatraemia (i.e. pts with either renal losses, on diuretics, or non renal losses – GI loss and third-spacing)

1. Fluid replacement/resuscitation is the priority, but it is still important not to correct sodium too quickly – no more than 10 mmol/L in the first 24 hours.

2. The diagnosis of hypovolaemia is a clinical one (based on tachycardia/ supine hypotension/ absent JVP / postural hypotension) and one should use normalisation of these same clinical parameters to judge success of resuscitation.

3. Use a relatively isotonic fluid for resuscitation such as Plasmalyte 148 ($[Na^+]$ – 140 mmol/L), Hartmann's ($[Na^+]$ – 131 mmol/L) or 'Normal Saline' (sodium chloride 0.9%); $[Na^+]$ – 154 mmol/L). Do not use hypotonic fluids as this will worsen the hyponatraemia.

4. Frequent checks of serum sodium are required during resuscitation (at least 4 hourly) to ensure correction is rate appropriate.

Note: Once the patient becomes euvolaemic, the non-osmotic stimulus for ADH production drops and the patient may become polyuric. In this setting, the serum sodium can quickly correct. It is vital that strict hourly input/output is measured during this period and frequent checks of serum sodium should continue. If the sodium is correcting too quickly, consideration of hypotonic fluids or use of desmopressin should be considered (see section 7 on IF HYPONATRAEMIA IS CORRECTED TOO RAPIDLY- page 9)

3.2. Guidelines for use of hypertonic sodium chloride 1.8%

1. A single aliquot of **300mls of sodium chloride 1.8% over 30 minutes** is recommended. The underlying cause of hyponatraemia must be investigated and treated.

a. Hypertonic sodium chloride 1.8% is licensed for administration via a central line and this is the preferred route of administration if the patient has central venous access.
b. However, if hypertonic sodium chloride 1.8% is required on an urgent basis, then **a peripheral cannula can be used** as the balance of risk is in favour of peripheral administration, rather than awaiting the inevitable delays (and risks) of central cannulation. A large cannula (minimum 18g/'green venflon') in a large vein in the antecubital fossa is strongly recommended and preferred over a smaller cannula in the back of the hand.
c. If peripheral venous access is used for hypertonic sodium chloride 1.8%, it must be clearly documented in the IV fluid prescription chart and patient's case notes and highlighted to nursing and junior medical staff so they are aware of the potential problems (mainly the risk of extravasation injury and necrosis). It should be recognised that this is an unlicensed use of hypertonic sodium chloride 1.8%.
d. Written instructions must be given to nursing staff to check the infusion site during and immediately after the infusion. The infusion must be stopped immediately if there is any evidence of extravasation at any point during the treatment. (See link for further NHSL guidance: http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/OOQS-TheOncologyOnlineQualitySystem/Documents/Non%20cytotoxic%20extravasation%20may%202010.pdf).

2. Serum sodium must be checked after the infusion (ensure biochemistry lab are aware of urgency of sample) and then a minimum of 4 hourly thereafter at least until the serum sodium is >125 mmol/L. Thereafter, 6 hourly monitoring may suffice until the serum sodium is ≥130 mmol/L (Frequent checks may still be required depending on the patient's clinical condition).

3. Further infusions of hypertonic sodium chloride 1.8% may be required and the **aim should be a 5 mmol/L increase** in serum sodium **with no more than a 10 mmol/L rise in the first 24 hours, and then 8 mmol/L rise every 24 hours thereafter.** (Therefore a second infusion should only be given once the post-infusion serum sodium level is known and further specialist endocrine/renal advice has been obtained).

4. Monitor urine output hourly. A sudden increase in urine output to >100 ml/hour signals increased risk of rapid correction of hyponatraemia as ADH activity becomes suppressed with correction of hyponatraemia resulting in greatly increased free water clearance. This would result in serum sodium concentrations rising more rapidly than expected.

4. CEREBRAL SALT WASTING SYNDROME (CSWS) AND SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION (SIADH)

4.1) Differentiating between CSWS and SIADH: It is difficult to differentiate between the two conditions, as the routinely measured biochemical parameters are often similar in both. A distinction can only be made on the basis of the patient's fluid status as CSWS leads to hypovolaemia due to natriuresis while SIADH is a euvolaemic condition.

a. ***CSWS*** is a cause of hyponatraemia in patients with CNS disease. Although it has most often been described in patients with subarachnoid haemorrhage, it remains an uncommon cause of hyponatraemia in this group of patients (with 7% due to CSWS compared to 69% due to SIADH in one series). Since IV (isotonic) sodium chloride

administration is part of standard treatment following a subarachnoid haemorrhage, hyponatraemia in these patients is more likely to be secondary to SIADH rather than CSWS in the majority of cases. It is important to note that interpretation of urine sodium results becomes difficult in such situations where IV sodium chloride has been administered. CSWS usually resolves spontaneously within 2 to 3 weeks of the cerebral insults, but it responds well to prompt treatment with IV sodium chloride 0.9%.

b. ***SIADH***: SIADH results from inappropriate elevation of levels of ADH. As a result, there is a decrease in the osmolality of fluid both in the intra and extra cellular compartments and hypo-osmolality ensues. Fluid restriction is the initial treatment.

Table 2 lists the characteristics of both conditions and may be used as a clinical guide to differentiate between the two.

Table 2

	CSWS	**SIADH**
Plasma sodium	Low	Low
Blood urea	Raised	Low or normal
Blood pressure	Low or postural hypotension	Normal
Central venous pressure	Low	Normal pressure
Urine sodium	May be significantly raised	Raised
Urine volume	High	Low
Thirst	Increased	Normal

4.2) Diagnosing SIADH:

SIADH is a diagnosis of exclusion. The criteria for diagnosing SIADH is summarised in table 3.

Table 3

1. Hypo-osmolality; plasma osmolality <275 mOsm/kg or plasma sodium <135 mmol/L
2. Inappropriate urinary concentration (Uosm >100 mOsm/kg) for hyponatraemia
3. Patient is clinically euvolaemic
4. Elevated urinary sodium (>30 mmol/L) with normal dietary salt and water intake
5. Exclusion of hypothyroidism, glucocorticoid deficiency[++], diuretic use
6. Normal renal, cardiac function

[++]The distinction between true SIADH and the hyponatraemia associated with ACTH/cortisol deficiency is particularly important in neurosurgical patients, who commonly develop hyponatraemia. For example, over 50% of patients with acute SAH develop hyponatraemia. This is often attributed to SIADH however studies have shown that a significant minority of long-term survivors of SAH develop permanent ACTH deficiency. Similarly, 16% of patients with acute head injury develop ACTH deficiency. **A SST MUST be done to exclude ACTH/glucocorticoid deficiency before a diagnosis of SIADH can be made**.

4.3) Aetiology of SIADH:

In addition to being associated with numerous conditions there are also many iatrogenic causes of SIADH (table 4). Clinical assessment and investigations must be targeted towards looking for a specific cause while treating the clinical manifestations of SIADH itself.

Table 4 (This list is not exhaustive)

Drug related • Drugs that stimulate release of ADH—nicotine, phenothiazines, tricyclic antidepressants, vinca alkaloids, cyclophosphamide, dopamine agonists, selective serotonin receptor inhibitors, opiates, thioxanthenes, haloperidol, oxytocin, MDMA ('ecstasy') • Drugs that potentiate the action of ADH or have direct renal effects—desmopressin (DDAVP™), cyclophosphamide, prostaglandin synthesis inhibitors, non-steroidal anti-inflammatories, paracetamol, carbamazepine • Mixed or uncertain actions--ACE-inhibitors, PPIs / omeprazole, melphalan
Pulmonary • Infections--TB, pneumonia, aspergillosis, empyema • Mechanical/ventilator causes—Adult respiratory distress syndrome, chronic obstructive pulmonary disease, positive-pressure ventilation
Tumours • Pulmonary/mediastinal • Duodenal, pancreatic, ureteral/prostate, uterine, nasopharyngeal, leukaemia
Central Nervous System disorders • Mass lesions • Inflammatory diseases • Degenerative/demyelinative diseases • Trauma--Subarachnoid haemorrhage, head trauma, pituitary stalk section • Miscellaneous--Acute psychosis, delirium tremens, hydrocephalus, transsphenoidal adenomectomy (as part of the 'triple phase response'→ initial cranial diabetes insipidus followed after 4-8 days by a transient remission or SIADH lasting 2-8 days followed by a recurrence of permanent diabetes insipidus).
Other causes • AIDS and AIDS-related complex • Prolonged strenuous exercise • Senile atrophy • Idiopathic

4.4) Types of SIADH:

- **TYPE A**: This is characterised by random hypersecretion of ADH. This is typically seen in small cell carcinomas of the lung. Plasma ADH levels remain inappropriately elevated and do not suppress with lowering of plasma osmolality. This is usually associated with severe hyponatraemia.

- **TYPE B:** This is characterised by elevated basal secretion of vasopressin despite normal regulation by osmolality.

- **TYPE C**: This is associated with the inappropriate release of ADH due to a 'reset osmostat' for ADH secretion. In these cases, ADH is released at an abnormally low threshold of plasma osmolality. There is a definable osmotic threshold for ADH release so lowering of plasma osmolality beyond this level or threshold leads to abolition of ADH secretion and protects against severe hyponatraemia. Cases of chronic hyponatraemia, particularly in the elderly, may fall into this category.

- **TYPE D**: A small number of patients with hyponatraemia have no demonstrable defect in the osmoregulation of vasopressin; this may be due to an activating mutation of the V2 receptor or due to abnormal control of aquaporin-2 water channels in renal collecting tubules or production of an antidiuretic principle other than AVP (correctly termed: syndrome of inappropriate anti-diuresis or SIAD).

4.5) Management of chronic hyponatraemia due to SIADH:

1. Withhold culprit medications
2. Identify and treat underlying cause
3. Obtain a chest x-ray in all patients with SIADH
4. If hyponatraemia unexplained and new (i.e. within last 12 months) then consider obtaining CT chest to exclude bronchogenic carcinoma even if CXR normal. (Several studies report that hypo-osmolality and hyponatraemia can pre-date radiographic abnormalities by 3-12 months)
5. Successful outcome depends on strict fluid restriction of 800-1000ml per day. Start with a 1000 ml fluid restriction.
6. If after fluid restriction for 3-4 days, the hyponatraemia does not begin to resolve then oral demeclocycline can be tried. 600-1200mg per day in divided doses can be commenced. Demeclocycline takes about 3-4 days to start to take effect and typically restores sodium levels within 5 to 14 days. Continue fluid restriction. [Note that demeclocycline are capsules and the contents are not suitable for NG/PEG administration. Therefore the capsules should not be opened and the contents administered via NG/PEG tubes. A suspension *[unlicensed]* can be ordered from pharmacy but this takes a few days to obtain].
   Monitor renal function daily while on demeclocycline and discontinue immediately if any sign of development of renal dysfunction.
7. Recent guidelines have recommended the use of a combination of loop diuretic and oral sodium chloride in the form of Slow-sodium™ tablets (e.g. 2 tablets three times daily) (or where administration via NG/PEG tube is required, sodium chloride 1mmol/ml oral solution *[unlicensed])* as an alternative to demeclocycline. (This combination treatment is more likely to work if the urine osmolality is over 350 mOsm/kg as this induces an increase in renal free water clearance).

5. CIRCUMSTANCES FOR USE OF TOLVAPTAN (V2 RECEPTOR ANTAGONIST)

Tolvaptan is a V2 receptor antagonist and is licensed for use in euvolaemic and hypervolaemic hyponatraemia. It should NOT be used to treat hypovolaemic hyponatraemia. It selectively antagonizes the antidiuretic effect of vasopressin by binding to V2 receptors in the kidney. This blockade will increase water loss without loss of electrolytes and therefore reduces total body water content while raising plasma sodium concentration. It is useful when hyponatraemia due to SIADH is biochemically severe but chronic with mild or moderate symptoms. However, its effects vary from patient to patient so for cases of acute, severe, symptomatic hyponatraemia, hypertonic sodium chloride is a better option.

There is little but increasing evidence regarding the use of V2 receptor antagonists in cases of severe hyponatraemia due to SIADH associated with cancer. A case series consisting of 12 patients with paraneoplastic SIADH showed high sensitivity to the use of tolvaptan for improving hyponatraemia. Another retrospective analysis of 45 cases had similar results.

6. GUIDELINES FOR USE OF TOLVAPTAN

1. Tolvaptan is not a formulary medicine, as it has not been approved for use in NHS Scotland, however, it can be obtained through the IPTR process in NHS Lothian, which requires an application to be submitted by the responsible consultant (see link: http://www.ljf.scot.nhs.uk/FormularyCommittee/Policies/Documents/IPTR%20Application%20Form%20(March%202014).docx). At present it is primarily recommended for cases of hyponatraemia due to SIADH secondary to underlying malignancy.
2. A daily dose of 7.5 mg is recommended to start with (This is half the licensed starting dose and is an off-label use of the preparation. Nonetheless, this dose is recommended at the start in order to avoid a rapid rise in sodium levels). This requires the tablets to be halved in pharmacy with a tablet halver, as the tablets are not scored. The dose needs reviewed on a daily basis with 4-6 hourly serum sodium checks initially until the correct dose for the individual patient is determined.
3. Avoid use in patients with underlying liver disease. Avoid use in renal failure and in anuric patients.
4. Its use is contraindicated if the patient is unable to sense or appropriately respond to thirst. If the patient has limited capacity to drink (e.g. oral/GI disease), glucose 5% may need to be initiated along with initiation of tolvaptan. This is particularly pertinent on day 1 of tolvaptan therapy as maximum aquaresis is observed then, when excess circulating water is greatest. More frequent checks of serum sodium (4,6,12 hourly) on day 1 of tolvaptan therapy may be advisable to exclude rapid correction of hyponatraemia (if by hour 6, the sodium has risen by 6 mmol/L then it is likely to rise by more than 10 mmol/L by hour 24. In such cases, water orally or glucose 5% intravenously should be given at hour 6 of treatment to slow down the rate of increase in serum sodium).
5. Discontinue demeclocycline while on tolvaptan.
6. Discontinue fluid restriction while on tolvaptan.
7. Do not use along with hypertonic sodium chloride 1.8%.
8. Tolvaptan is metabolized via the cytochrome p450 pathway therefore enzyme inducers/inhibitors should be avoided or used with caution, and dose adjustments made where required. [Refer to summary of product characteristics for detailed advice: http://www.medicines.org.uk/emc/medicine/22210]

9. Careful (4-6 hourly) monitoring of sodium is required once on tolvaptan as the rate of increase in plasma sodium should not exceed 10 mmol/L in 24 hours. If it does, then co-administration of hypotonic fluid may be required.
10. Monitor LFTs (An increased risk of liver injury was seen in trials involving this drug). If LFTs begin to get deranged, immediately stop the drug and monitor for signs of liver failure.
11. Tolvaptan should be discontinued once symptoms resolve AND/OR serum sodium normalises. However, sudden discontinuation of tolvaptan may result in a relapse of hyponatraemia therefore the dose may need to be tapered down as sodium levels rise and fluid restriction may need to be reinstated, especially if the underlying cause of SIADH (e.g. malignancy) has not resolved.
12. Serum sodium must be checked daily after discontinuation of tolvaptan until sodium levels stabilise.

7. IF HYPONATRAEMIA IS CORRECTED TOO RAPIDLY

1. Prompt intervention for re-lowering the serum sodium concentration if it increases >10 mmol/L during the first 24 hours or >8 mmol/L any 24 hours thereafter, should be made.
2. Discontinue on-going active treatment for hyponatraemia.
3. Consult endocrine/renal team and consider a sodium-free intravenous infusion of 10mL/kg body weight of electrolyte-free fluid (such as glucose 5%) over 1 hour under strict monitoring of urine output and fluid balance.
4. Consult endocrine team to discuss if it is appropriate to add IV desmopressin (DDAVP™) 2 micrograms (not repeated more frequently than every 8 hours).

8. RENIN MEASUREMENT

Renin levels correlate with volume status and would be useful in differentiating between hyponatraemia due to mild hypovolaemia and SIADH. However, delay in acquiring a result makes it an inappropriate diagnostic tool in the acute setting.