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Diagnosis and management of hyponatraemia in the older patient

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Abstract

Hyponatraemia (serum sodium concentration below 135 mmol/L) is the most common electrolyte disturbance and occurs commonly in older people. The causes can be complex to diagnose and treat and many published guidelines do not focus on the issues in an older patient group. Here, we are principally concerned with diagnosis and management of euvolaemic and hypervolaemic hyponatraemia in hospitalised patients over 70 years old. We also aim to increase awareness of hyponatraemia in residential aged care facilities and the community.

Hyponatraemia can have many causes; in older people, chronic hyponatraemia can often be the result of medications used to treat chronic disease, particularly thiazide or thiazide-like drugs (such as indapamide) or drugs acting on the central nervous system.

Where a reversible trigger (such as drug-induced hyponatraemia) can be identified, hyponatraemia may be treated relatively simply. Chronic hyponatraemia due to an irreversible cause will require ongoing treatment. Fluid restriction can be an effective therapy in dilutional hyponatraemia, although poor compliance and the burdensome nature of the restrictions are important considerations.

Tolvaptan is an oral vasopressin receptor antagonist that can increase serum sodium concentrations by increasing electrolyte-free water excretion. Tolvaptan use is supported by clinical trial evidence in patients with hypervolaemic or euvolaemic hyponatraemia below 125 mmol/L. Clinical trial evidence also supports its use after

a trial of fluid restriction in patients with symptomatic hyponatraemia above 125 mmol/L with symptoms. The use of tolvaptan is affected by regulatory restriction of chronic therapy due to safety concern, and the non-subsidised cost of treatment.

Key words (5 words in order of importance): Hyponatraemia, aged, frail elderly, tolvaptan

Introduction

Hyponatraemia is the most common electrolyte disturbance in both hospitalised patients and in the community. It is particularly prevalent in frail older people. Over 40% of elderly patients admitted to intensive care experience hyponatraemia at some time during their hospitalisation,[1] and chronic hyponatraemia has been observed in 18% of aged care residents.[2] The causes of hyponatraemia are multiple and varied.[3] Age-related comorbidities, polypharmacy, and age-related physiological changes add complexity often resulting in suboptimal management in older patients.

Some published guidelines for determining the cause and management of hyponatraemia do not specifically address the issues in the older patient group. This may result in suboptimal diagnostic work-up and consequently poor treatment of geriatric patients with mild to moderate hyponatraemia.

High level evidence to support recommendations for diagnosis and treatment of hyponatraemia is lacking. Further research on functional outcomes is required, particularly in older patients. There is emerging evidence that even mild, apparently asymptomatic hyponatraemia has the potential to contribute to cognitive impairment, bone demineralisation, increased length of hospital stay, institutionalisation and increased mortality.[4-6] Improvement in serum sodium concentration in hyponatraemic patients has been shown to be associated with a reduction in overall mortality,[7] although this may not be a causative association. Given there are no randomised controlled trials (RCTs) demonstrating that the correction of

hyponatraemia improves clinically-important outcomes, it remains unknown whether hyponatraemia is a causative contributor, or merely a sensitive biomarker of poor health-related outcomes.

Here we present currently-available evidence and the opinion of an expert panel of Australian geriatricians and endocrinologists on the management of hyponatraemia in older people. We aim to increase the awareness and management of hyponatraemia both in hospitalised people aged over 70 years, with mild to moderate hyponatraemia, and in people living in residential aged care facilities and in the community.

Severity of hyponatraemia and symptoms

The normal serum sodium concentration is 135 mmol/L to 145 mmol/L. The cut-off concentrations for the definitions of mild, moderate and severe hyponatraemia vary slightly between guidelines.[8-10] Here we define mild hyponatraemia as sodium concentrations from 130 to 135 mmol/L, moderate hyponatraemia as 125 to 130 mmol/L, 120 to 125 mmol/L as moderately severe if there are no acute symptoms, otherwise below 125 mmol/L is severe, and less than 120 mmol/L as always severe.

Mild hyponatraemia is often considered to be asymptomatic, yet has been shown to be associated with subtle cognitive impairments, to which older patients may be more vulnerable. Symptoms such as mental confusion, gait disturbance, impaired consciousness and seizures may occur with increasing severity of hyponatraemia.

Acute symptomatic hyponatraemia is a medical emergency. Immediate treatment is required in the setting of significant central nervous system (CNS) symptoms and should not be delayed pending a diagnosis of the cause of hyponatraemia. In severe symptomatic hyponatraemia, intravenous hypertonic saline is often used to increase the serum sodium concentration.

Diagnosis of hyponatraemia

Diagnosis of the underlying cause of hyponatraemia to determine the appropriate treatment can be complex, particularly in older people (Figure 1), in whom the cause is often multifactorial. In this article, we are principally concerned with euvolaemic/hypervolaemic hyponatraemia, i.e. dilutional hyponatraemia, with decreased serum osmolarity. Hyponatraemia associated with severe hyperglycaemia, and pseudohyponatraemia with severe dyslipidaemia should be excluded at the outset (Figure 1). Multiple contributing factors may need to be identified to reach a diagnosis and provide appropriate treatment. Common causes of non-hypovolaemic hyponatraemia include medications (in particular thiazide and thiazide-like diuretics), and the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

In a large Australian study of 255 older patients (mean age of 72 years) admitted to hospital with an initial serum sodium concentration of 120 mmol/L or less, the commonest causes were thiazide/indapamide diuretics (41%), SIADH (38%) and hypovolaemia (24%).[11]

Medical history, examination and investigations

It is axiomatic that a thorough medical history should be taken. Chronic hyponatraemia is often caused by medications prescribed for management of

chronic disease. A careful medication history to exclude drug-induced hyponatraemia is essential before investigating other causes of hyponatraemia.

Before diagnosing SIADH, other reversible conditions must be specifically excluded. Hypovolaemia is addressed by assessing hydration status; however, clinical examination is often unreliable and there is no reliable biomarker of hydration. A urine sodium concentration less than 30 mmol/L is consistent with hypovolaemia, but a higher urine sodium does not exclude hypovolaemia (Figure 1). Impaired excretion of free water (e.g. in the setting of pain or nausea, inadequate plasma volume, low cardiac output and renal impairment) is an important mechanism in many older patients with hyponatraemia. Hyperglycaemia causes a non-hypotonic hyponatraemia via a shift of water into the extracellular fluid. Other treatable causes of hyponatraemia include hypoadrenalism and hypothyroidism. Therefore, initial investigations should include blood tests for glucose, lipids, cortisol, thyroid function, liver function and plasma osmolality and urine tests for osmolality, sodium and potassium concentrations.

Common causes of hyponatraemia are outlined in Table 1.

SIADH

CNS-active drugs such as antipsychotics, antidepressants, anticonvulsants, opiates and some cancer drugs may cause SIADH.[9] Disease processes known to cause SIADH include pulmonary abnormalities (carcinoma, abscess, empyema, pneumonia

etc), cerebral space occupying lesions, other CNS disorders and other malignancies. Frequently, the cause is idiopathic in older patients.[12]

Other considerations in older people

Frailty is an important consideration in older people. Hyponatraemia occurring in the context of frailty may add to the burden of illness in an older person and increase the risk of cognitive decline, falls and functional impairment.[13]

Older people are also more likely to have comorbidities known to cause hyponatraemia such as congestive cardiac failure, renal failure, cirrhosis, respiratory infections, dehydration, neurological disease (including stroke) and malignancies.

The decision about whether to treat mild to moderate hyponatraemia should take into consideration the potential for improvement in other domains (such as cognition, or reduction in length of hospital stay). It seems reasonable to consider treating mild hyponatraemia even if apparently asymptomatic, to try to optimise function in a frail older person and improve quality of life. However, there is currently no high-level evidence that correction of mild hyponatraemia leads to improvements in clinically-important outcomes.

Approach to treatment

If a reversible trigger for hyponatraemia such as drug-induced hyponatraemia can be identified, treatment is relatively simple. Chronic hyponatraemia due to an irreversible cause will often require ongoing treatment.

Safe withdrawal of drugs that may cause hyponatraemia

Medications should be reviewed. Where practical, drugs that may cause hyponatraemia should be ceased.

Careful follow-up is required where drugs are ceased, to monitor for re-emergence of the condition that was being treated. For example, hypertension may recur on withdrawal of a thiazide diuretic. In this setting, it is advisable to monitor the patient for 12 months with a monthly review during the first six months and thence every two or three months during the second six months. In older patients, hypertension has been shown to be much slower to return than in younger patients upon withdrawal of antihypertensive therapy.[14]

Medication

There are many medications that can cause hyponatraemia,[15] with diuretics and CNS-active drugs being the most common. Diuretic-induced hyponatraemia is predominantly caused by thiazide or thiazide-like drugs such as indapamide.

Selective serotonin reuptake inhibitors (SSRIs) are more frequently associated with hyponatraemia than other antidepressant drugs. Older age and concomitant use of diuretics are important risk factors for SSRI-induced hyponatraemia.

Carbamazepine, and valproic acid can induce hyponatraemia, as can antineoplastic agents such as vincristine, vinblastine, cisplatin and cyclophosphamide. Use of non-

steroidal anti-inflammatory drugs (NSAIDs) by patients who are volume depleted, or in those with SIADH increases the risk and severity of developing hyponatraemia.

Proton pump inhibitors only very rarely cause hyponatraemia.

Treatment of non-reversible SIADH

If no underlying reversible cause for SIADH is identified (e.g. medication, infection, intercurrent illness), ongoing treatment to raise sodium concentrations may be required. This can either be achieved by reducing fluid intake, or by increasing urine volume (hence allowing a less strict fluid restriction) by provision of solute such as sodium chloride or urea or by stimulating aquaresis with vaptans. Solutes such as sodium chloride may be given because, when ADH concentrations are persistently elevated, urine volume is primarily determined by excreted solute.

Fluid restriction

Fluid restriction can be an effective therapy in dilutional hyponatraemia (euvolaemia or hypervolaemia). However, if prolonged beyond a few days, as is often the case, poor compliance and reduced quality of life are important considerations, especially in older patients who may not be drinking much before fluid restriction is imposed. Long-term fluid restriction for chronic mild to moderate hyponatraemia can be particularly burdensome for patients and, while temporarily successful, is often limited by non-compliance.

Fluid restriction has limited utility in other situations. For example, often patients are encouraged to drink more in the setting of a urinary tract infection.

Salt supplementation and loop diuretics / urea

In patients with SIADH there is a limited role for use of oral sodium chloride. In dilutional hyponatraemia salt supplementation is rarely if ever associated with a meaningful improvement and nausea and vomiting can occasionally result in compromising adherence. The intravenous administration of isotonic saline can worsen hyponatraemia if the urine osmolarity remains fixed higher than plasma osmolarity as is typical in SIADH, which results in the excretion of the administered sodium in a lower water volume than in which it was given. This will lead to net free water retention and worsening hyponatraemia. Likewise, the effect of oral sodium supplementation depends on the concomitant water intake.

Similar to sodium chloride, urea is also recommended in some guidelines to increase urine volume, however its use is limited by non-palatability, and no standardised formulation is available in Australia.

Tolvaptan

Vaptans are a class of oral vasopressin receptor antagonists that increase serum sodium concentrations by increasing electrolyte-free water excretion.[16] By antagonising ADH action at the vasopressin receptor, they directly target the pathophysiology of SIADH. They are contra-indicated in hypovolemic

hyponatraemia which requires volume repletion instead. A systematic review of known interventions for treatment of chronic non-hypovolaemic hypotonic hyponatraemia, identified that RCT evidence is lacking for treatments other than vaptans.[17] A meta-analysis of the RCTs showed that vaptans are more effective than placebo for outcomes related to serum sodium by an average of approximately 5 mmol/L on average. There is a need for more evidence on outcomes relating to quality of life.

Tolvaptan is an orally active selective vasopressin V_2-receptor antagonist with a higher affinity for the V_2-receptor than endogenous arginine vasopressin. Tolvaptan is the only vaptan approved for use in Australia and is indicated for the treatment of clinically significant hypervolaemic or euvolaemic hyponatraemia including in patients with heart failure and SIADH.[18] Clinically significant hyponatraemia is defined as serum sodium concentration less than 125 mmol/L, or less marked hyponatraemia that is symptomatic and has resisted correction with fluid restriction. Participants in the tolvaptan SALT trials[19] had mild to modest hyponatraemia (mean 129 mmol/L). The effectiveness of tolvaptan in severe hyponatraemia has not been well studied. In emergency setting such as impending cerebral oedema, hypertonic saline is indicated, because the onset of action of tolvaptan (2 to 4 hours) is too slow (Table 2).

The Australian Product Information states that treatment with tolvaptan should be initiated and re-initiated in hospital because of the need for dose titration with close

monitoring of serum sodium concentration and volume status. Treatment with tolvaptan should be initiated at a dose of 15 mg once daily, with escalation to a maximum of 60 mg once daily as tolerated to achieve the desired level of serum sodium. Tolvaptan should not be administered for more than 30 days to minimise the risk of liver injury. Tolvaptan should only occasionally (and cautiously) be used concurrently with other strategies to increase serum sodium (e.g. fluid restriction) as this increases the risk of overly rapid sodium correction.

Patient management should include the following

1. Hospitalisation during commencement of tolvaptan
2. Discontinuation of other therapeutic modalities intended to raise serum sodium (e.g. discontinuation of fluid restriction)
3. Monitoring of serum electrolytes, initially 6-hourly for the first 24 hours and continuing at least daily over the next several days.
4. Discontinuation or interruption of tolvaptan therapy in patients who experience too rapid a rise in serum sodium. In extreme cases administration of hypotonic fluids should be considered. Serum potassium concentration may increase, especially in patients with baseline serum potassium concentration of more than 5 mmol/L, and in those receiving drugs known to increase serum potassium concentration.

5. Advice to patients to resume fluid restriction following discontinuation of tolvaptan with monitoring for changes in serum sodium concentration and volume status.

Tolvaptan is not reimbursed by the Australian Government through the Pharmaceutical Benefits Scheme, so the cost to the patient (about $80 per day) is an important consideration once discharged from hospital.

Clinical trials of tolvaptan

Tolvaptan has been studied in patients with euvolaemic or hypervolaemic hyponatraemia in two randomised double-blind placebo controlled phase 3 studies, SALT-1 and SALT-2,[19] and in an open-label long-term extension study, SALTWATER.[20] Oral tolvaptan or matching placebo were administered once daily as an adjunct to standard therapy. Standard therapy included non-mandatory fluid restriction but excluded demeclocycline, lithium chloride or urea.

Serum sodium concentrations increased more (by about 5 mmol/L) in the tolvaptan group than the placebo group during the first four days and after the full 30 days of therapy. Fluid restriction was also required by more patients in the placebo group than the tolvaptan group (25% vs 14%, $p<0.01$). However, hyponatraemia recurred in the week following discontinuation of tolvaptan. Side effects of tolvaptan included thirst, dry mouth and urinary frequency. Rates of discontinuation were similar for patients receiving tolvaptan (10%) and placebo (12%).

The safety profile of tolvaptan has been evaluated in over 4000 patients in open-label or placebo controlled trials, of which approximately 650 patients had hyponatraemia.[18] Events of any severity that occurred at a rate of at least 2% more in tolvaptan-treated patients than in patients on placebo were dry mouth, constipation, thirst, asthenia, pyrexia, hyperglycaemia, anorexia and pollakiuria or polyuria.[18]

Liver injury has been observed in clinical trials investigating a different indication with long-term use of tolvaptan at higher dose than for hyponatraemia. Duration of therapy is therefore limited to 30 days, and use should be avoided in patients with underlying liver disease, including cirrhosis, because the ability to recover from liver injury may be impaired. In the open label SALTWATER extension trial with 12 months of follow-up, tolvaptan was effective over this time period.

The mental component of the SF-12 general health status assesses vitality, social functioning, emotionally limited accomplishment, calmness and sadness. In the pooled SALT-1 and SALT-2 results there was a modest improvement in mental status that was statistically significant but of uncertain clinical importance.[19] An unplanned sub-analysis of patients with SIADH in the SALT-1 and -2 studies found similar efficacy and safety results in the subgroup as in the pooled studies, but greater improvement in the physical component of the SF-12 health survey compared to the overall mixed aetiology patient group.[21] Patients with SIADH were

identified in the study based on a clinical diagnosis of SIADH by the individual study investigators, rather than laboratory results.

A post hoc analysis found a statistically significant reduction in length of hospital stay with tolvaptan compared to standard care in patients with SIADH and other diagnoses (excluding congestive heart failure and cirrhosis) (mean difference -3.7 days, p=0.045). However, non-prespecified post hoc analyses of RCTs should be viewed with caution and primarily be considered as hypothesis-generating rather than as definitive evidence. Further research to investigate the reasons for this difference is warranted.

Recommendation

Due to the unsatisfactory nature of current treatment with either fluid restriction or solutes to increase urine volume, and the evidence from phase III RCTs, tolvaptan should be considered within the current TGA approved indication. Further research needs to be conducted to examine its longer-term use to influence clinically important endpoints in older people, including cognition and function. Use of tolvaptan should be considered if the patient has SIADH and there is no acute reversible trigger that can be targeted, such as withdrawal of thiazide diuretics or treatment of infection, and the hyponatraemia has resisted correction with fluid restriction (see treatment algorithm in Figure 2). Overshoot correction of hyponatraemia is of concern[22] and careful monitoring of serum sodium is recommended, 6-hourly for the first 24 hours and continuing at least daily over the

next several days. A treatment plan should be in place for patients once they discontinue tolvaptan as hyponatraemia is likely to return.

Demeclocyline

Demeclocycline has been used as a chronic treatment for hyponatraemia. Demeclocycline is no longer routinely available in Australia. There is limited availability though the Special Access Scheme. There is a lack of evidence from RCTs for demeclocycline, and the incidence of the known hepatotoxic and nephrotoxic side effects is unclear but appears to be low. Onset of action and efficacy is unpredictable and only 50% of patients respond.

Conclusions

Hyponatraemia is common in older people on admission to hospital, and in residential aged care facilities. Diagnosis of the underlying cause of hyponatraemia which is necessary to provide optimal treatment may be complex in the older patient as the aetiology is often multi-factorial. Management is further complicated by the fact that many treatment strategies have limited efficacy and are not supported by robust evidence. Moreover, although the current data are suggestive, there is a lack of high level evidence linking the correction of mild hyponatraemia to functional outcomes.

Reversible causes, such as medication-induced hyponatraemia, are treated by addressing the underlying cause. Fluid restriction can be an effective short-term

therapy in euvolaemic or hypervolaemic hyponatraemia; however, poor compliance and reduced quality of life are important considerations in chronic therapy. Tolvaptan is so far little used in Australia, but is a treatment option with clinical trial evidence and should be considered in patients with non-hypovolaemic hyponatraemia below 125 mmol/L or in patients with hyponatraemia above 125 mmol/L with symptoms, with initial hospitalisation and frequent electrolyte monitoring. The use of tolvaptan is constrained by regulatory restriction of chronic therapy due to safety concerns, and the non-subsidised cost of this therapy.

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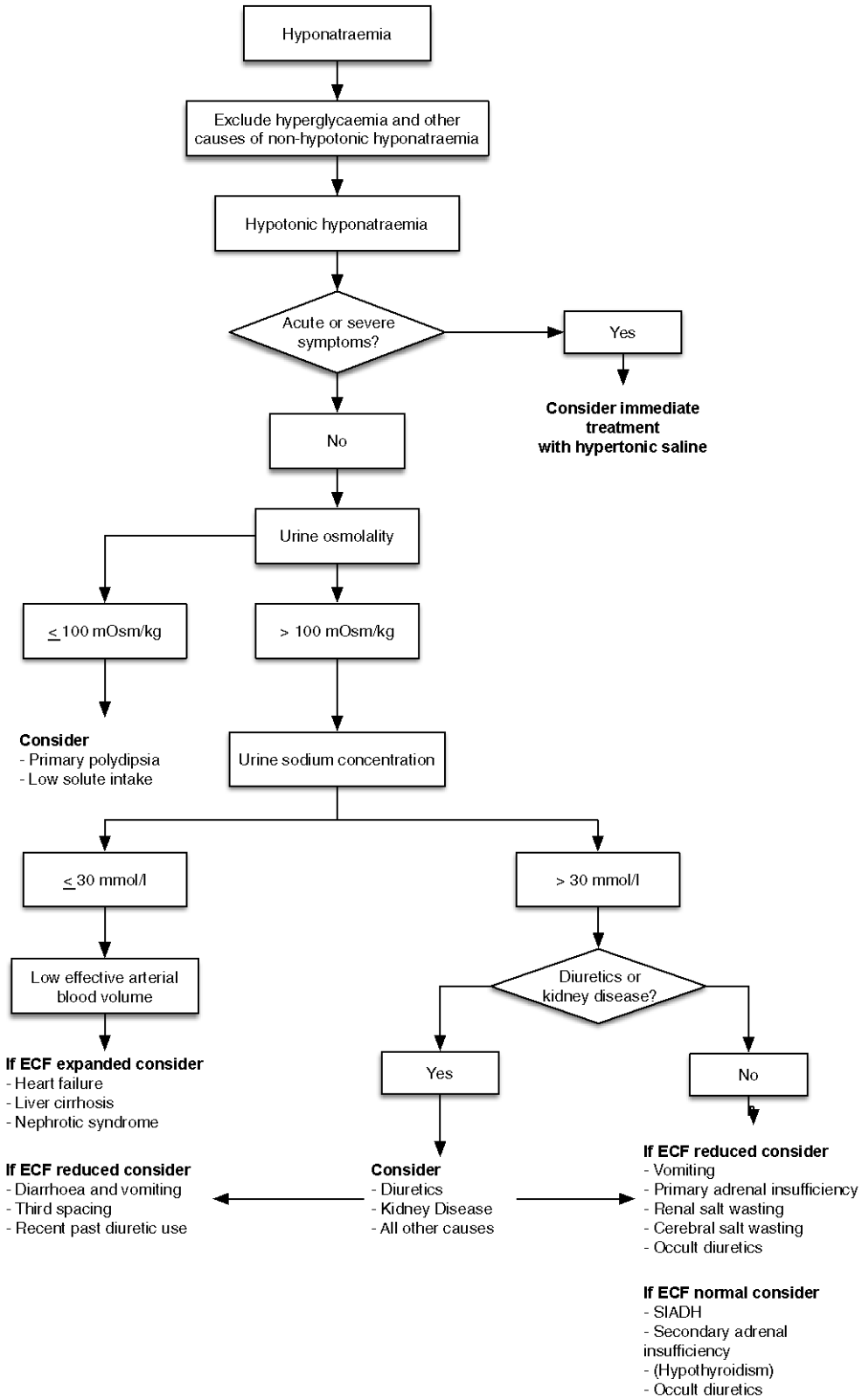
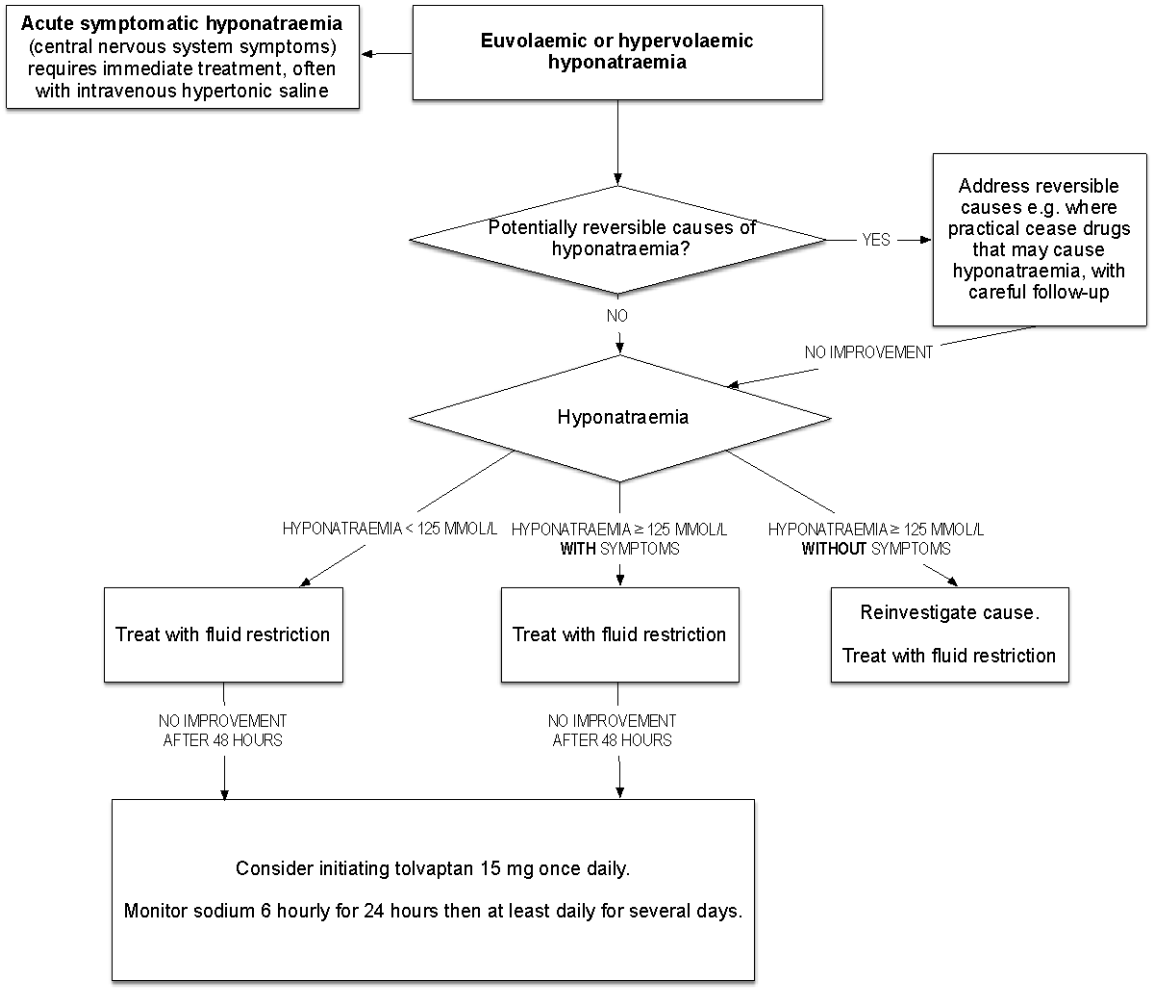
Figure legends

Figure 1 Algorithm for the diagnosis of hyponatraemia (based on Spasovski 2014)[8]



ECF: extracellular fluid; SIADH: syndrome of inappropriate anti-diuretic hormone

Figure 2 Treatment algorithm for euvolaemic or hypovolaemic hyponatraemia



Note: Tolvaptan dose can be escalated to a maximum of 60 mg once daily as tolerated to achieve the desired sodium level. Tolvaptan should not be administered for more than 30 days.

Tables (each table on a separate page complete with title and footnotes)

Table 1: Contributing causes of hyponatraemia (based on Soiza 2014)[3]

Hypovolaemic hyponatraemia
- Inadequate fluid intake or replacement - Diuretic therapy - Diarrhoea and vomiting - Pancreatitis/third space loss of fluids - Renal salt wasting - Burns and skin losses - Mineralocorticoid deficiency
Euvolaemic hyponatraemia
- Syndrome of inappropriate anti-diuretic hormone (SIADH) - Medications (e.g. hydrochlorothiazide, indapamide, carbamazepine, paroxetine, venlafaxine) - Hypothyroidism (primary or secondary) - Polydipsia - Fluid loss with inappropriate fluid (salt) replacement - Glucocorticoid deficiency (hypoadrenalism, hypopituitarism)
Hypervolaemic hyponatraemia
- Cardiac failure - Cirrhosis - Chronic kidney disease

- Acute kidney injury
- Nephrotic syndrome

Table 2 Summary of tolvaptan pharmacokinetics in healthy subjects

PK parameter	
t_{max}	2 to 4 hours
Onset of action	2 to 4 hours (Specifically, aquaretic and sodium increasing effect)
Peak effect	Between 4 and 8 hours[+]
Absolute bioavailability	About 56%. Coadministration with food has no effect on plasma concentrations.
Clearance pathways	Extensively metabolised by the liver. Elimination entirely by non-renal routes, mainly metabolised by CYP3A. After oral dosing, clearance is about 4 mL/min/kg
$t_{1/2}$	Terminal half-life is about 8 hours; steady state concentrations obtained after first dose. Tolvaptan has linear pharmacokinetics for doses of 15 to 60 mg.
[+] Increase of ~6 mmol/L in serum sodium concentration and ~9 mL/min increase in urine excretion rate. Approximately 60% of the peak effect on serum sodium concentration is sustained at 24 hours post dose, but the urinary excretion rate is no longer elevated by this time.	