Mild hyponatraemia... not so innocuous

Linda Bryant MClinPharm, PGPdHospPharmAdmin, PhD, FNZHPA, FNZCP, FPSNZ, MCAPA

KEY POINTS

• Even mild hyponatraemia (serum sodium concentration of 130 to 134 mmol/L) may cause clinically important effects such as gait disturbance, reduced concentration and muscle cramps.

• Commonly prescribed medicines that cause hyponatraemia included thiazides, SSRIs, proton pump inhibitors and ACE inhibitors, and when combined may result in a cumulative effect.

• Mild hyponatraemia should be addressed and any potential medicines causing or exacerbating hyponatraemia should be discontinued if their long-term benefit is limited compared to the impact of the hyponatraemia.

There is a tendency to accept mild hyponatraemia in the older person because it is relatively common and considered normal, having developed over some time, and with some adaptation over time. Mild hyponatraemia is a serum sodium concentration of 130 to 134 mmol/L. Although the symptoms may be subtle, they may be clinically important for an older person (Table 1), particularly the tendency to fall and reduced concentration. There are a number of pathological causes for hyponatraemia, but one that may cause a dilemma is drug-induced hyponatraemia because of the need to balance the need for the drug versus the risk of the subtle symptoms of mild hyponatraemia.

In one study of elderly people presenting with fragility fractures, hyponatraemia was seen in 26% of cases. Dehydration and the prescription of thiazides and proton pump inhibitors were the commonest potentially causative factors. The incidence of drug-induced hyponatraemia is difficult to quantify, as often it is only moderate to severe hyponatraemia that is reported, or studies are based on hospitalisation with hyponatraemia. The incidence is also related to coexisting risk factors, particularly age and female gender (Table 2).

Diuretics

Thiazides are considered the most common cause of hyponatraemia, with an estimated incidence of up to 5%. The primary mechanism is due to the renal effect of thiazides on sodium and water homeostasis, with increased antidiuretic hormone (ADH) being rare.

Loop and potassium-sparing diuretics may also cause hyponatraemia, but less frequently than thiazides. The mechanism for loop diuretics involves the loop of Henle rather than the cortex of the distal tube where thiazides act. There is minimal clinical difference between the thiazides as causative agents, and indapamide is included in this class effect. There may be a dose/potency-related effect. Onset of hyponatraemia with thiazides is usually within two weeks, but may occur at any time, particularly in susceptible people as their medical condition changes, such as during a respiratory or gastrointestinal illness. In particular, care is required when adding other medicines that may cause hyponatraemia, such as proton pump inhibitors, antidepressants and ACE inhibitors (Table 3). ACE inhibitors, particularly in combination with thiazides, are reported to cause hyponatraemia.

Table 1. Symptoms of hyponatraemia

| • Gait disturbance  
| • A tendency to fall  
| • Muscle spasms and cramps  
| • Reduced concentration  
| • Tiredness  
| • Nausea  
| • Headache |

Table 2. Risk factors for drug-induced hyponatraemia

| • Increasing age  
| • Lower body mass index (BMI)  
| • Female gender  
| • Multiple medicines that may cause hyponatraemia  
| • Pre-existing conditions—hypothyroidism, congestive heart failure, respiratory infections (pneumonia), some neoplasms |
**Action**

- Stop the thiazide and use an alternative blood pressure–lowering medicine.
- If a loop diuretic is suspected of causing hyponatraemia, due to the different tubular site of action water retention and the development of hyponatraemia will be limited, unless distal delivery is very low or water intake is very high. Monitor serum electrolytes and symptoms of hyponatraemia closely.

**Antidepressants**

Selective serotonin reuptake inhibitor (SSRI)–induced hyponatraemia was well reported soon after the introduction of SSRIs, but hyponatraemia may also occur with tricyclic antidepressants, as the mechanism appears to be a central increase in ADH and an increased effect of ADH. The onset is usually within the first four weeks of antidepressant initiation, although it may be as long as three months. Resolution of hyponatraemia occurs within two weeks of stopping the antidepressant.

People with the cytochrome P450 2D6 polymorphism that classes them as poor CYP 2D6 metabolisers appear to be more at risk of hyponatraemia. The incidence of this polymorphism may be up to 0.5% of the population.

**Proton pump inhibitors**

Proton pump inhibitor (PPI)–induced hyponatraemia may occur within two weeks of initiation of treatment and is usually dramatic, but may also result in a gradual reduction in serum sodium concentration over several months.

**Antiepileptic medicines**

There is a relatively high rate of antiepileptic drug–induced hyponatraemia of up to 5%. The proposed mechanism appears to be a centrally mediated increase in ADH and an enhanced effect. For carbamazepine, there appears to be a correlation between the extent of hyponatraemia and the serum concentration, as well as the rate at which the dosage is increased.

**Other medicines potentially causing hyponatraemia**

Antipsychotics may cause hyponatraemia, but care is required to discount primary polydipsia as a cause. Opiates generally are associated with hyponatraemia but tramadol may have an added effect.
risk, due to its additional serotonin reuptake inhibitor activity. Rarely, NSAIDs may potentiate the effect of ADH through reduced water excretion, but this is usually due to an additive effect, such as with dehydration.

Cumulative effects
One of the problems with multiple medicines in older people is that there can be a cumulative effect of the medicines. Single medicines may precipitate moderate to severe hyponatraemia when used alone, but for some people the effect of individual medicines may be small but there is a cumulative effect. Be cautious when adding medicines known to induce hyponatraemia, particularly thiazides, and monitor for subtle effects of hyponatraemia.

Suggested actions
As even mild hyponatraemia may cause clinically important effects, such as gait disturbances, a tendency to fall, weakness and reduced concentration, it is preferable to review and, ideally, stop any medicine that could potentially cause hyponatraemia. For the very elderly, the perhaps limited long-term benefit of continuation of the medicine needs to be balanced against the subtle but important effects of mild hyponatraemia.

Practice point—adjusting serum sodium concentration for high blood glucose concentrations
For people with a high serum glucose, add 2.4 mmol/L to the measured serum sodium concentration for every 5.5 mmol/L incremental increase in serum glucose concentration above the standard 5.5 mmol/L.

References