

Drug Induced Hyponatraemia

Hyponatraemia may be drug-induced. A review of drug therapy is essential in patients presenting with low serum sodium concentrations. However, there are also several medical causes of hyponatraemia and it is important to note that in some patients, multiple factors may contribute to a low serum sodium concentration.

Hyponatraemia is defined as a serum sodium concentration $<136\text{mmol/L}$, although symptoms rarely appear above 120mmol/L . Hyponatraemia may be associated with high, normal or low plasma osmolality. Drug-induced hyponatraemia is generally low osmolality (hypotonic) and is usually due to:

- increased sodium loss as occurs with thiazide diuretics; and/or,
- decreased water loss as occurs with increased concentrations of antidiuretic hormone (ADH).

Assessment of drug-induced hyponatraemia requires measurement of serum and urine osmolality, plus serum and urine sodium concentrations.

Hyponatraemia associated with diuretics

Thiazide diuretics are responsible for almost all severe diuretic-induced hyponatraemia (serum sodium concentration $<115\text{mmol/L}$). Thiazides act in the cortex of the kidney in the distal tubule to cause sodium (and therefore water) and potassium excretion. Volume depletion leads to ADH secretion and enhanced water reabsorption. This can result in the excretion of urine with high sodium and potassium concentrations and directly promote the development of hyponatraemia independent of water intake.

Loop diuretics may also lead to volume depletion, but are less frequently associated with hyponatraemia (possibly due to their different actions in the kidney).

Hyponatraemia due to increased ADH

SIADH stands for "Syndrome of Inappropriate AntiDiuretic Hormone". It describes increased ADH secretion (for various reasons) and is presumed in the presence of low serum sodium and serum osmolality, along with high urine osmolality in the absence of adrenal insufficiency, hypothyroidism, or other organ failure. A number of drugs have been suggested to cause increased ADH secretion, but as the data is predominantly collected from case reports, the actual incidence in the general population is unknown.

Several centrally acting drugs have been associated with hyponatraemia due to increased ADH secretion. The molecular mechanism is thought to involve serotonin agonism and dopamine antagonism.

Carbamazepine appears to be the most reported and investigated drug as a cause of increased ADH. Several other **anticonvulsants** have been associated rarely with hyponatraemia but their mechanism is less clear.

Antidepressants are frequently associated with hyponatraemia. The most commonly reported drugs currently are the selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, but this may reflect more frequent use. Tricyclic antidepressants are also frequently implicated, and it appears that all antidepressants may cause hyponatraemia.

Antipsychotics, including the typical (eg haloperidol, chlorpromazine) and atypical (eg olanzapine, risperidone) have been associated with hyponatraemia.

ACE inhibitors, and some cytotoxic drugs such as **vinca alkaloids** and **cyclophosphamide**, are also associated with hyponatraemia. This is also due to increased ADH, but the ADH appears to be a response to the drugs' effects on the kidney, rather than direct central mechanisms.

NSAIDs (non-steroidal anti-inflammatory drugs) and **sulphonylureas** appear to induce hyponatraemia via potentiation of ADH rather than increased ADH secretion.

Exogenous forms of ADH such as **vasopressin**, and **desmopressin** may also lead to low serum sodium.

Hyponatraemia via other causes

Other commonly used drugs such as omeprazole and benzodiazepines have been associated with hyponatraemia, but the mechanisms are unclear.

In summary: Drug-induced hyponatraemia is generally associated with sodium loss (as occurs with diuretics) or increased ADH effect. Drug-induced hyponatraemia usually occurs in the first two weeks of drug therapy. Discontinuation of the suspected drug usually results in an improvement of serum sodium concentrations within two weeks, although resolution may take up to 28 days in cases where the patient has significant co-morbidities. It is important to note that although low serum sodium may be drug-induced, treatment of contributing medical causes such as hypothyroidism, may allow the use of drugs that had previously caused hyponatraemia.