

Medicinal mishap

Severe hyponatraemia due to mirtazapine

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Case

A 79-year-old woman was admitted with new onset confusion. Her past medical history included heart failure and depression. On admission she was taking ramipril, metoprolol and frusemide. She had started mirtazapine 10 days previously.

The patient was euvolaemic. Her initial investigations revealed a low serum sodium of 113 mmol/L, low serum osmolality 243 mmol/kg (normal range 275–295 mmol/kg) and inappropriately high urine osmolality of 170 mmol/kg (normal range 50–1200 mmol/kg). Tests showed normal renal, thyroid and adrenal function. A diagnosis of inappropriate antidiuretic hormone secretion was suspected. Her chest X-ray and CT of the head did not show evidence of lesions potentially responsible for inappropriate secretion of antidiuretic hormone.

The patient's fluid intake was restricted, and frusemide and mirtazapine were ceased. Her confusion began to resolve after four days. Her serum sodium improved to 132 mmol/L by day 10. Frusemide was reintroduced, without a fall in serum sodium over the next few weeks. We therefore suspected that mirtazapine had caused her hyponatraemia.

Comment

Mirtazapine is a tetracyclic analogue of mianserin used to treat major depression. It is well documented that many psychotropic drugs can cause hyponatraemia, but there are only two published case reports involving mirtazapine.^{1,2} The Adverse Drug Reactions Advisory Committee has received 18 reports since the drug became available in Australia.

Mirtazapine exerts its therapeutic effect by increasing the release of noradrenaline and serotonin by blockade of α_2 adrenoceptors. This increases the level of both substances within the brain. There are animal data suggesting that serotonin acts on the hypothalamic supraoptic nucleus to increase secretion of antidiuretic hormone. This results in impaired free water excretion and hypo-osmolar hyponatraemia³ and might be a mechanism by which mirtazapine has this effect.

Patients who may be at risk of drug-related hyponatraemia are the elderly, those who have comorbidities (such as chronic congestive cardiac failure, alcoholic liver disease, intracranial pathology) or those taking other drugs (thiazides, ACE inhibitors) which are associated with hyponatraemia (see box).

We consider that measurements of serum and urine osmolality, urine sodium, thyroid, adrenal and renal function are indicated when severe (sodium < 125 mmol/L) and symptomatic hyponatraemia develops, even if the patient has just started a new drug. Complete and prompt reversal on cessation of the drug and the exclusion of other causes support the diagnosis. Confirming the diagnosis would require a rechallenge with mirtazapine, but this may be inappropriate given the risks to the patient and the availability of many alternative antidepressants.

Conclusion

Symptoms of severe hyponatraemia include confusion, weakness, lethargy, convulsions and coma. Hyponatraemia may be an under-reported adverse effect of mirtazapine which can result in hospitalisation. Clinicians should be aware of the possibility, particularly as early symptoms may mimic those of the patient's depression. We suggest patients with risk factors (see box) have a serum sodium measured before and 1–2 weeks after starting mirtazapine, or at any time if symptoms suggestive of hyponatraemia develop.

Risk factors for mirtazapine-induced hyponatraemia⁴

- Advanced age
- Female gender
- Pre-existing hyponatraemia or comorbidities associated with hyponatraemia
- Concurrent drugs which can cause hyponatraemia

References

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