

## Medicinal mishaps

### Serotonin syndrome

#### Case

An elderly woman presented to hospital with a painful left hip following a fall. She was usually mobile and cared for herself, but she had a history of depression and panic disorder. On examination she was alert and orientated, but X-rays confirmed a left intertrochanteric fracture. Surgery was planned for the next day so she was started on intravenous fluids and traction. She was prescribed tramadol 100 mg four times daily in addition to her usual treatment of paracetamol 1 gm four times daily, fludrocortisone 0.05 mg in the morning, sertraline 200 mg at night, pericyazine 2.5 mg twice daily, and latanoprost eye drops at night.

On the night of admission she was drowsy but her speech was coherent. Preoperatively she was noted to be confused and unable to give a history. She remained confused postoperatively and developed visual and auditory hallucinations.

On the third postoperative day the nursing notes queried bilateral foot drop with spasms of both feet.

Six days after admission her mental state deteriorated (minimal mental examination score was 19/30). She had a low grade fever with plantar flexion and inversion of both feet with rigidity, tremor and dystonia. A psychiatrist diagnosed a serotonergic syndrome, precipitated by sertraline and tramadol. Tramadol, sertraline, pericyazine and fludrocortisone were ceased.

Despite treatment with benserazide/levodopa and botulinum toxin the woman had persisting disability due to contractures in her legs and feet. A full clinical assessment and relevant investigations showed no other abnormalities to account for this disability. It is possible that her disability had resulted from contractures developing as a result of prolonged dystonia caused by serotonergic syndrome.

#### Comment

Tramadol is an analgesic with agonist action on the  $\mu$  opioid receptor. It also inhibits noradrenaline and serotonin reuptake.

Serotonin syndrome is caused by excess serotonin in the central nervous system (CNS). It commonly occurs as an interaction between two drugs, where each drug causes a rise in serotonin concentration in the CNS. The classic example is a combination of a selective serotonin reuptake inhibitor and a monoamine oxidase inhibitor, but it has occurred with selective serotonin reuptake inhibitors and tramadol.

Signs and symptoms of serotonin syndrome vary but may include change in mental status and behaviour, motor system changes and autonomic instability. Distinguishing them from depression

or the adverse effects of antidepressants may be difficult.<sup>1</sup> Three or more of the following signs must be present after commencing or increasing the dose of a serotonergic agent:

- mental status changes, confusion, hypomania, agitation
- inco-ordination
- myoclonus
- hyperreflexia
- diaphoresis
- shivering
- tremor
- diarrhoea
- fever.

Other aetiologies (e.g. infections) need to be excluded.

Clinically, serotonin syndrome is likely to be under-reported because it is often not recognised or may be confused with neuroleptic malignant syndrome; symptoms may be mild, moderate or severe. Serotonin syndrome appears to be self-limiting, resolving quickly when the offending drugs are discontinued, but occasionally it may be fatal.

#### Recommendations

All patients should have a full medication history taken before being prescribed tramadol. Any drug that increases serotonin levels by any mechanism should raise the possibility of an interaction (see box). This situation is most likely to arise in patients being treated for depression.

#### Drugs to avoid in combination with tramadol

selective serotonin reuptake inhibitors (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram)  
tricyclic antidepressants  
moclobemide  
St John's wort (hypericum)  
venlafaxine

#### REFERENCE

1. Tiller JWG. Medicinal mishaps: serotonin states. *Aust Prescr* 1998;21:63.

#### FURTHER READING

Tramadol alert. Interaction with antidepressants may lead to serotonin syndrome. NSW Therapeutic Assessment Group. *TAGNET Bulletin* August 2000;5:5-6.

<http://www.clininfo.health.nsw.gov.au/nswtag/publications/index.html>

Tramadol and serotonin syndrome. *Aust Adv Drug React Bull* 2001;21:14.