CASE REPORT

Trazodone in the elderly: risk of extrapyramidal acute events

Joana Sotto Mayor, Ana Paula Pacheco, Sofia Esperança, Antonio Oliveira e Silva

Department of Internal
Medicine, Hospital de Braga,
Braga, Portugal

Correspondence to
Dr Joana Sotto Mayor,
s.mayor.joana@gmail.com

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SUMMARY

Trazodone is a second-generation atypical antidepressant exercising selective inhibitory action on the transport of serotonin. It also has an antagonist effect, similar to nefazodone, on the 5HT₁ and 5HT₂ receptors, probably due to the therapeutic effects of such substances. It is very effective in the treatment of depression, in anxiety and insomnia. Its known side effects mainly occur with prolonged use of daily doses of 150–200 mg. The ability to enhance drowsiness may be associated with some risk in elderly patients. This clinical case illustrates an acute extrapyramidal event induced by a low dose of trazodone.

BACKGROUND

This case is important because it alerts the scientific community to an unexpected adverse drug effect induced by a low trazodone dose, especially relevant in the geriatric population.^{1–4}

CASE PRESENTATION

An 84-year-old man with hypertension, medicated daily with perindopril + indapamide 10+2.5 mg and acetylsalicylic acid 150 mg, presented to the emergency department (ED) with a 1-month history of evolving altered mental status with disorientation, slurred speech, generalised weakness, irritability (muscle fatigue in the lower limbs), intermittent headache and episodes of amnesia. He had no symptoms related to genitourinary, gastrointestinal or respiratory disorders, and denied chest pain or fever. On examination, the patient was oriented both in time and space, with slurred speech; the remaining physical and neurological examination was normal. Blood work showed serum sodium of 117 mmol/L with remaining results within normal parameters. Head CT scan did not show evidence of acute ischaemic or haemorrhagic disturbances. The patient was admitted to the internal medicine department for aetiological study of symptomatic hyponatraemia. The indapamide was stopped and the patient was started on a sodium chloride infusion associated with his normal dose of perindopril and acetylsalicylic acid.

On the second day of hospitalisation, with serum sodium of 121 mmol/L, the patient reported insomnia, for which trazodone was started at a dosage of 100 mg at night, with no other therapeutic alterations. Two days later, the patient developed sudden mental status alteration with increased drowsiness and marked spasticity, with *cogwheel* rigidity of the upper and lower limbs.

INVESTIGATIONS

New blood work showed serum sodium of 127 mmol/L, rejecting this as the cause of the patient's symptoms. Also, a new head CT scan excluded acute ischaemic or haemorrhagic lesions, which, if present, could have justified the patient's symptoms.

TREATMENT

With an acute extrapyramidal syndrome in mind as a possible diagnosis, 5 mg of biperiden intravenously were given with slow but progressive reversal of muscular symptoms. Repeated administration of the same dose 30 min later, led to full recovery of the patient's usual mental status. Trazodone was immediately suspended and the patient did not present with any more neurological symptoms. After the observed improvement after biperiden and maintenance of normal neurological examination after interrupting treatment, we attribute this episode to a trazodone-induced acute extrapyramidal event.

DISCUSSION

Although it is known that the prolonged use of trazodone may induce parkinsonian symptoms,^{3,4} the descriptions found in the literature are rare with low-dose drug administration (100 mg intradermally) and in such a short period of time (2 days). To support this fact, we have the following data: (1) the patient was not under any other sedation therapy; (b) a clear temporal relationship existed between the introduction of trazodone and the onset of symptoms and (c) recurrence of extrapyramidal symptoms was absent after discontinuation of trazodone. The authors are not aware of other cases described in the literature of an acute extrapyramidal event induced with a low dose of trazodone for such a short period of time. In this case, the patient presented with parkinsonian generalised hypertonia similar to an opisthotonos.

The mechanism by which trazodone induced the occurrence of an acute extrapyramidal event is explained by the fact that this drug (which belongs to the large group of selective inhibitors of serotonin reuptake (SSRIs)) increases serotonin activity, giving a clinical picture that is neurologically characterised by a disturbed state of consciousness, with confusion, rigidity and hyper-reflexia.⁴

Thus, the main treatment of an acute extrapyramidal event induced by serotonergic drugs is the discontinuation of the drug, as this can by itself be sufficient for complete recovery within 24 h.⁴

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An extensive literature review shows few reports of drug interactions of trazodone with other drugs, and with trazodone metabolism and interaction on the cytochrome P450 system. Secondary pharmacodynamic synergy interactions mainly relate to the potentiation of the sedative and hypotensive effect.² Thus, the combined use of trazodone with antihypertensives and depressants of the central nervous system (CNS) must always be monitored.

With clonidine, for example, the literature shows reductions in antihypertensive effect and increased risk of CNS depression. The ability to enhance the drowsiness and sedation associated with psychomotor impairment puts older people at higher risk, including the danger of falls and bone fracture with subsequent complications. Also the synergistic interaction with bupropion could apparently facilitate the outbreak of seizures.

There are few descriptions that show change in anticoagulation effects resulting from concomitant use of warfarin and trazodone.

Some reports indicate that serotonergic syndrome (SS) is a possible complication when trazodone is used concurrently with any medication capable of enhancing serotonergic transmission.

The SS mechanism is understood to be due to an excess of serotonin available in the CNS acting on 5HT1A. The literature shows interactions in the association of trazodone with paroxetine, sertraline, fluoxetine and venlafaxine.²

In 2003, Greenblatt *et al*⁵ researched the possible association between trazodone and ritonavir, an antiretroviral drug that inhibits CYP 3A4, showing that there was an exacerbation of the side effects of trazodone in patients who simultaneously received ritonavir, especially increased sedation and fatigue associated with elevated plasma concentrations of trazodone, and the extension of its half-life.²

Imatinib and amiodarone may increase plasma levels of trazodone, with risk of syncope and hypotension by inhibiting hepatic metabolism, while carbamazepine can reduce trazodone levels for hepatic induction. It should also be noted that the use of SSRIs can induce hyponatraemia due to inappropriate antidiuretic hormone secretion, especially in the elderly.⁶ In a retrospective study in a psychiatric ward for the elderly,⁷ hyponatraemia after the use of SSRI occurred in 25% of patients. Between 1980 and 1995, 736 cases were reported, and in the majority of these, hyponatraemia developed within 3–120 days after starting therapy, usually when in combination with fluoxetine.⁸ Cases with trazodone interaction were not reported.

Hyponatraemia manifestations are mainly neurological, due to cerebral oedema. Indeed, these patients may be asymptomatic, or they may present with symptoms ranging from headaches and nausea to convulsions, coma and death, depending on the degree of hyponatraemia and speed of assimilation.^{9 10} However, the authors are not aware of the occurrence of hyponatraemia-induced parkinsonism.

Learning points

The authors report this case for its rarity, seeking to alert clinicians to consider the ratio between risk and benefit when introducing psychiatric drugs. This is especially true in the elderly, in whom the side effects of these therapies may be substantially exacerbated and produce significant morbidity.

Competing interests None declared.

Patient consent Obtained.

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