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Serotonin syndrome in advanced cancer patient treated with tramadol and antidepressants

Abstract

Serotonin syndrome is potentially life-threatening syndrome associated with excessive serotonergic activity within the central nervous system. Serotonin syndrome is associated with medication use, drug interactions, and overdose. While serotonin syndrome is often associated with the use of selective serotonin inhibitors (SSRI), an increasing number of reports are being presented involving the use of tramadol. With tramadol increasing popularity, the goal of this article is to make physicians more alert and aware of this potential side effect. Serotonin syndrome may be difficult to diagnose. A case of serotonin syndrome caused by the combination of tramadol and antidepressants in a patient with advanced cancer is presented and discussed. The importance of early diagnosis of this syndrome is emphasized.

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Key words: tramadol, toxicity, serotonin syndrome, antidepressants

Introduction

Tramadol is used for the treatment of moderate pain in adults. Structurally it is not an opioid but it binds to μ receptors. It is a prodrug metabolized by CYP2D6 isoenzyme of cytochrome P450 and the analgesic effect results from O-demethylation whose product is M1 [1–3]. Its opioid agonist action is combined with parent compound effect which is the inhibition of the reuptake of serotonin (5-HT) and norepinephrine.

Phenotypic variation influences the rate of accumulation and elimination of the drug. This supposes an uncertainty of the effect that the patient is going to have, both in terms of efficacy as in terms of adverse effects. Tramadol is a substrate for the cytochrome P450 CYP2D6 liver enzyme, hence any agents with the ability to inhibit this enzyme will probably interact with tramadol and may intensify its adverse effects. In addition, genetic polymorphism of CYP2D6 may result in a wide spectrum of enzyme activity (phenotypes). At one end of the spectrum, two inactive alleles lead to individuals with no CYP2D6 enzyme activity, so-called poor metabolizers, which may lead to inadequate analgesia due to lack of formation of M1. At the other extreme, duplication of alleles results in individuals with very high CYP2D6 enzyme activity (ultrarapid metabolisers) that may lead to excessive adverse effects intensity [1–3].

There is a growing amount of post-marketing evidence that shows risks with the consumption of tramadol, which should make the decision to prescribe this drug to be considered more carefully. Between 1997 and 2017, 30,730 cases of adverse effects were reported to the FDA. If tramadol is administered with

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drugs that inhibit CYP2D6, such as paroxetine or fluoxetine, a patient can pass from being an extensive or intermediate metabolizer to a poor metabolizer with risks of developing a serotonin syndrome [3]. This syndrome has high mortality and results from the interaction between drugs. Although classified as an opioid, only about 30% of tramadol activity can be reversed with naloxone and it is these non–opioid actions that set tramadol apart from other drugs. However, it is also the serotoninergic and noradrenergic effects that give tramadol its most troublesome reported side–effects: sedation, lowering the convulsion threshold, and delirium [1, 2].

Case presentation

A 56-year-old patient with a recent diagnosis of stage IV pancreatic cancer with hepatic metastases who received paroxetine 20 mg/day and mirtazapine 30 mg at night for treatment of a depressive syndrome. Five days before admission, she developed pain in the lower back and epigastrium, numerical rating scale (NRS) 6/10, and her doctor started treatment with tramadol 100 mg every 8 hours and paracetamol 1 g every 8 hours. Three days after starting this treatment, her family perceived her confused, she had intense pain, palpitations, diarrhoea, nausea and profuse sweating. The pain intensity was increasing (NRS 9/10) and the clinical situation of delirium, profuse sweating, tachycardia and pain motivated the admission into a Palliative Care Unit.

At the physical examination the patient showed a hyperactive delirium, with CAM (confusion assessment method) test positive, sweating, HR 110/ min, BP 170/95 mm Hg, RR 24/min, axillary temperature 37°C. She demonstrated generalized muscle rigidity with hyperreflexia in the lower extremities. Spontaneous and ocular clonus. Bilateral mydriasis. Normal cardiopulmonary auscultation. Abdomen painful, without peritonism. Hepatomegaly 2 cm. Analytical: Sodium 138 mMol/L, potassium 4 mMol/L, chloride 94 mMol/L, creatinine 1.2 mg/dL, creatinine clearance 60 mL/min, level 26 mcg/mL, WBC 10.5 thou/mcL, HGB 11.0 gm/dL, MCV 101 FL, AST 60 U/L, AST 70 U/L, GGT 120 U/ ml. Normal liver function tests. Plasma calcium corrected: normal. Negative urine culture. EKG sinus rhythm, Rx chest normal, cranial CT normal.

Discussion

The serotonin syndrome for associating tramadol plus paroxetine plus mirtazapine was a diagnosis of exclusion in the absence of evidence of infectious, metabolic or ischemic causes. It was decided to discontinue tramadol and mirtazapine and paroxetine was gradually lowered. Parenteral hydration was initiated with 1500 ml/24 hours. The patient was treated with midazolam at low doses (10 mg/24 hours) and 4 days after starting this treatment she began to improve. The delirium reverted and the clonus remitted. The blood pressure and heart rate normalized. Good analgesia was achieved with low doses of subcutaneous morphine (15 mg/24 hours).

The prevalence of serotonin syndrome caused by tramadol is unknown, however between 1997 and 2017 968 cases of serotonin syndrome were reported to the FDA, 98 of which died [5]. The true incidence of serotonin syndrome is not known because it is not reported. This lack of notification has many reasons: the manifestations are usually falsely attributed to other causes, in moderate cases most of the clinicians do not suspect it, and in a study done among doctors 85% did not know this diagnosis [5].

The serotonin syndrome is diagnosed clinically by anamnesis and physical examination. The Hunter criteria can help; they have 84% sensitivity and 97% specificity. The patient must have taken a serotonergic agent and show one of the following signs: spontaneous clonus, inducible clonus with agitation or diaphoresis, ocular clonus with agitation or diaphoresis, ocular clonus with hypertonia and hyperthermia and/or tremor with hyperreflexia (Table 1) [4, 5].

Serotonin syndrome includes a classic triad of neuromuscular hyperactivity, autonomic hyperactivity and delirium. Moderate cases present with nonspecific symptoms such as nervousness, insomnia, nausea, tachycardia, abdominal pain and it is often underdiagnosed and undertreated [5]. In mild cases, as in the present case, patients present with mild hypertension and tachycardia with some combination of mydriasis, diaphoresis, shivering, tremor, myoclonus, and hyperreflexia. In severe cases, hyperthermia is greater than 41°C with delirium and muscle rigidity. Severe cases may result in coma and death by many complications, such as seizures, rhabdomyolysis, myoglobinuria, metabolic acidosis, renal failure, acute respiratory distress syndrome, respiratory failure, and diffuse intravascular clotting [4, 5]. It has been reported frequently when associating tramadol with other drugs such as fluoxetine, paroxetine, sertraline, venlafaxine, citalopram and bupropion. This is also a problem if tramadol is co-administered with monoamine oxidase inhibitors and some atypical antipsychotics [4, 5]. In this patient who was receiving paroxetine and mirtazapine, the serotonin syndrome manifested when tramadol was added. To be able to make the diagnosis, a complete and thorough medical history is necessary.

Table 1. Symptoms of serotonin syndrome

Serio-usness	Autonomic signs	Neurological Signs	Mental status	Other
Mild	• Afebrile or low-grade fever • Tachycardia • Mydriasis • Diaphoresis or shivering	• Intermittent tremor • Akathisia • Myoclonus • Mild hyperreflexia	• Restlessness • Anxiety	
Moderate	• Increased Tachycardia • Fever (40°C) • Diarrhoea with hyperactive bowel sounds • Diaphoresis with normal skin colour	• Hyperreflexia • Inducible clonus • Ocular clonus (slow continuous lateral eye movements) • Myoclonus	• Easily startled • Increased confusion • Agitation and hypervigilance	• Rhabdomyolysis • Metabolic acidosis • Renal failure • Disseminated Intravascular coagulopathy (secondary to hyperthermia)
Severe	• The temperature often more than 41°C (secondary to increased tone)	• Increased muscle tone (lower limb > upper) • Spontaneous clonus • Substantial myoclonus or hyperreflexia	• Delirium • Coma	• As above

The prevention of serotonin syndrome begins by sensitizing physicians to be able to recognize early the first signs and symptoms of serotonin toxicity and suspend the precipitating agents. Most physicians are aware of serotonin syndrome secondary to antidepressants but do not think of other drugs such as analgesics. Tramadol has an analgesic effect that does not exceed moderate and there is no robust evidence for its use. The aforementioned adverse effects require prudent use or prescription should even be avoided [5].

In the treatment of cancer–related pain, the second step of the WHO analgesic ladder is under questioning since the criticism that is given is the definitive absence of proven efficacy of "weak" opioids. A meta-analysis of randomized trials showed no significant differences between non-opioid analgesics alone or non–opioids combined with opioids. A Cochrane review on the use of tramadol in the treatment of cancer-related pain, which included 10 studies with 958 participants, stated that there is limited, very low quality of evidence from randomised controlled trials that tramadol produced pain relief in some adults with pain due to cancer and no evidence at all in children; the place of tramadol in managing cancer pain and its role as step 2 opioid of the WHO analgesic ladder is unclear [6]. Given these data on the doubtful efficacy of tramadol in treatment of oncological pain, many authors have proposed the abolition of the second step of the WHO analgesic ladder, in favour of the early use of morphine in low doses [7].

Conclusions

Concurrent administration of tramadol with SSRIs or SNRIs appears to increase the risk of serotonin syndrome. In patients who may require higher doses of tramadol, it would be reasonable to avoid the combinations [4, 5]. Until there is a substantial body of evidence of either benefit or harm, doctors will continue to prescribe tramadol based on personal preference rather than clinical evidence. Mechanistically, tramadol does have some appealing properties, despite adverse effects, so cautious use, starting with a small dose and careful titration are suggested.

Henry Marsh, in his book "Do no harm", describes the complex calculation involved in decision making, always weighing the possibility of treating patients in the face of the danger of aggravating their situation; put on one side of the scale the knowledge and experience and, on the other, the risks. We can admit that the iatrogenic damage is not avoidable in absolute terms, but it is in relative terms, and it is convenient to analyse what can be done to reduce it to the minimum.

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