

Codeine Precipitating Serotonin Syndrome in a Patient in Therapy with Antidepressant and Triptan

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The serotonin syndrome is a serious medical condition due to an intensive stimulation of serotonin receptors. It is a rare, but severe, consequence of interaction between serotomimetic agents. This is a report of a 70-year-old woman steadily in therapy with venlafaxine and rizatriptan for migraine and major depressive syndrome. She was admitted to neurology unit for decreased light reflex with miotic pupils, global hyperreflexia, tremor, anxiety, ataxia and incoordination. The patient was diagnosed as a probable case of serotonin syndrome due to a pharmacological interaction between venlafaxine and rizatriptan triggered by opioid intake. In this paper, the development of symptomatology, the clinical examination and the possible pharmacokinetics explanation were carefully discussed and analysed.

KEY WORDS: Drug–drug interactions; Codeine; Serotonin syndrome; Prescription drug misuse; Migraine disorders; Major depressive disorder.

INTRODUCTION

Drug interactions are nowadays a very serious problem and they can frequently include common prescribed drugs and over-the-counter (OTC) medicines.^{1,2} Antidepressants are very frequently prescribed drugs, they include selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs), prescribed for the treatment of major depressive disorder.³

The SSRIs mechanism of action is to increase the intra-synaptic level of serotonin with the inhibition of serotonin reuptake. The same is true for SNRIs respect to noradrenaline. As a secondary mechanism of action, SSRIs increase efficacy of 5-hydroxytryptamine (5-HT) neurons by desensitizing 5-HT autoreceptors of the serotonin nerve terminals.^{4,5}

Adverse events (AEs) of SSRIs and SNRIs include: hyponatremia, risk of ischemic stroke and intracranial hemorrhages,⁶ suicidality and mania.⁷ The serotonin syn-

drome (SS) is an example of AE, induced by drug interaction; it is a rare consequence of interaction between serotomimetic agents. The SS is considered to be due to an intensive stimulation of 5-HT_{1A} (in central grey nuclei and in the medulla) and of 5-HT_{2A} (in the central and peripheral nervous system) receptors by serotonergic medicines⁸; it is characterized by neuromuscular hyperactivity (myoclonus and hyperreflexia), cognitive alterations (agitation and confusion) and autonomic disorders (hyperthermia and tachycardia).⁹ The SS is caused by the serotonergic agent's use and it usually occurs within 24 hours after the serotomimetic drugs intake.⁸⁻¹⁰ Abadie *et al.*¹¹ described the mostly involved medicines in SS, based on the French pharmacovigilance reports; SSRIs seem to be involved in 42.1% and SNRIs (mainly venlafaxine) in 9.1%.

Triptans (5-HT receptor agonists) are another drug category selectively acting on the serotonin receptors. Triptans are 5-HT_{1B/1D} receptor agonists with lower affinity also for 5-HT_{1A} and 5-HT_{2A} receptors,¹² they are used in migraine's therapy and they usually have dose-dependent side effects (paresthesia, nausea, fatigue, dry mouth and facial flushing).^{13,14}

We report a case of SS probably induced by interaction between one antidepressant and one triptan with codeine.

Codeine, 3-methylmorphine, is a natural methylated form of morphine. Codeine is metabolized into morphine

Received: January 19, 2017 / **Revised:** February 22, 2017

Accepted: March 16, 2017

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(and its metabolites) and into codeine-6-glucuronide and norcodeine; the principal cytochromes involved in metabolic codeine pathway are CYP2D6 and CYP3A4.¹⁵⁾ Worldwide codeine, in combined preparation with acetaminophen, is the most commonly opiate prescribed used in the treatment of mild to moderate pain and as an anti-tussive medicine, indeed in different countries (i.e., United Kingdom, South Africa, Ireland, France, and Australia) is an OTC medicine.¹⁶⁻¹⁸⁾ The AEs of codeine are the same of those of opioid category (sedation, nausea, vomiting, constipation and respiratory depression).¹⁹⁾

The aim of this report is to describe an interesting and not yet reported AE observed in one patient steadily in therapy with venlafaxine and rizatriptan. We have analyzed the development of symptomatology after added therapy with codeine and the possible association with opioid treatment.

CASE

The patient is a 70-year-old woman, she has a long clinical history of migraine and major depressive syndrome. She describes tension-type headache and depressive syndrome with anxiety and insomnia since she was 20 years old.

During the last 10 years she was treated with individual support psychotherapy and she received several psychopharmacological therapies, such as valproate, topiramate, propranolol and amitriptyline (as a long term therapy), acetaminophen, indomethacin, or other non-steroidal anti-inflammatory drugs (as needed medications). Migraine attack, major depressive disorder and analgesic drugs misuse were the main reasons for her hospital admissions.

On November 21, 2015, due to a severe migraine attack she took for the first time in her life codeine 30 mg in combination with acetaminophen 500 mg. In that moment, she was prescribed with venlafaxine 225 mg/day (150 mg in the morning and 75 mg in the afternoon) and diazepam 5 mg/three times a day (recommended dose). Nevertheless she reported, over the past few months that she also took, without any medical supervision, rizatriptan 10 mg as needed use. Her drug intake was basically as needed use and she demonstrated a poor compliance with prescribed medications and doses, but, to the best of our knowledge, she never became dependent to any illicit substances, neither to opiate medications or alcohol.

Around 30 to 36 hours after her first codeine intake she contacted a general practitioner reporting symptoms as nervousness, irritability, agitation, mania, confusion,

tremor, diaphoresis and nausea. On November 23, she was hospitalized.

The inpatient parameters was: body temperature 37.5°C; pulse 100 beats/minute; blood pressure 140/90 mmHg and respiratory rate 21 breaths/minute. Complete blood test (including liver and kidney function tests, creatinine kinase, and serum electrolyte values) were all within normal limits and also the electrocardiogram resulted in the normal range. During the neurological examination it was detected: miotic pupils with decreased light reflex, global hyperreflexia, tremor in both hands, ataxia and incoordination. She had tremors in both hands and anxiety during the interview. No lateralizing neurological signs were observed. The neuropsychological test MODA (Milan Overall Dementia Assessment) was performed and the total score was 87.7/100 (with an age and education adjusted score of 88.5/100),²⁰⁾ so the test score results in the normal limits. Cranial computed tomography scan were normal and it did not reveal any significant vascular abnormalities.

Venlafaxine and codeine were immediately stopped and endovenous hydration was started with saline solution 0.9%. Diazepam 5 mg was continued orally twice a day for agitation. Approximately 8 hours after the discontinuation of venlafaxine and codeine, the described symptoms disappeared and her hypervigilance improved. Five days later the patient was discharged.

DISCUSSION

The SS is a predictable response to the increase of serotonin neurotransmission, due to a serotonin drug-drug interaction²¹⁾ as well as to an individual vulnerability.²²⁾ In humans the increased risk of developing the SS is hypothesized by Gelener *et al.*¹⁰⁾ with a possible serotonin transporter polymorphism.

The SS, following concomitant triptan and SSRI (or SNRI) use, is biologically possible. Both of these medications increase serotonin transmission, therefore, it is predictable that their concomitant use would result in higher serotonin activity.^{4,8,11)} The combination of agitation, diaphoresis, tremor and hyperreflexia in our patient led clinicians to hypothesize a diagnosis of SS, according to Sternbach criteria²³⁾ and Hunter criteria.²⁴⁾ Specifically agitation, diaphoresis, tremor and confusion are the Sternbach criteria detected in the patient. Tremor and hyperreflexia are the Hunter criteria observed.

We hypothesize that the development of the SS is connected to the interaction with venlafaxine and rizatriptan

triggered by codeine.

It is also reasonable to suspect that the symptomatology described was associated with an acute opiate poisoning and/or withdrawal. However, in our opinion the opiate intoxication seems to be less probable because the physicians didn't observe any somnolence, bradycardia, hypotension or bradypnea (inpatient parameters: 100 beats/minute; 140/90 mmHg; 21 breaths/minute). In the same perspective the opiate withdrawal doesn't seem more likely because the patient never stop to ingest codeine, netheir other opiate substances.

As previously mentioned the concomitant use of SSRIs/SNRIs and triptans²⁵⁾ could induce the SS: the United States Food and Drug Administration Alert²⁶⁾ reporting the potential for life-threatening SS in patients taking SSRIs/SNRIs and triptans concomitantly. This information is based on 27 cases of SS occurring in patients treated with concomitant SSRI or SNRI and triptans.

After a systematic literature review on Medline/PubMed database we have discovered several cases of SS induced by a combination of antidepressants plus triptans, or antidepressants plus opioids,²⁷⁾ especially tramadol.²⁸⁻³¹⁾ The tramadol involvement in the SS is probably due to the mechanism of action: it binds to mu opioid receptors but also inhibits the monoamine (norepinephrine and 5-HT) reuptake.^{28,32,33)} Contrary to synthetic piperidine (i.e., fentanyl³⁴⁾ and tramadol²⁸⁻³¹⁾, codeine, a phenanthrene, does not work as a serotonin uptake inhibitor.^{33,35,36)} Several authors^{35,36)} reported that morphine analogues may potentially increase the intrasynaptic serotonin levels with some unknown mechanisms.

We will propose, as a possible pathophysiological explanation, for the development of SS the cytochromes (CYP2D6 and CYP3A4) involvement,^{14,36)} as also reported by Direk.⁹⁾ The genetic individual vulnerability may offer an additional and explanation.⁹⁾ Additionally, there are few reports^{37,38)} indicating that opiates may differentially modulate 5-HT neurotransmission in the central nervous system.

As mentioned in the introduction, the metabolite morphine, wich has a high affinity for the mu opioid receptor, is primarily responsible for positive and negative effects of codeine therapy. Althrough the amount of morphine metabolized from codeine is not the same for everybody. This interindividual variability is in part due to the polymorphic cytochrome CYP2D6 enzyme (the mediator of codeine transformation into morphine). As reported by Tao and Auerbach,³⁸⁾ morphine infusion into the dorsal raphe nucleus of rats increased extracellular 5-HT in the nu-

cleus accumbens. So, one of the possible pathophysiological explanation of this SS case is the iper-biotransformation of codeine into morphine, mediated in this patient by a high CYP2D6 activity. This mechanism could explain the increase of 5-HT and the consequent trigger role of codeine in our patient, already in therapy with SNRI and triptan.

In conclusion, SS is a severe clinical condition with high mortality. Physicians should be aware of all serotonergic agents prescription.

To the best of our knowledge there are no reports of serotonin toxicity triggered by codeine in a patient in therapy with venlafaxine and rizatriptan was never reported. SS should be kept in mind if patients are in therapy with all substances that may interact with serotonergic drugs through the CYP450 pathway,³⁹⁾ including OTC medications and illicit substances. Moreover meticulous collection of AEs by patients, doctors and pharmaceutical companies should be necessary to investigate in more detail the underlying causes of severe pharmacological interactions.

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