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CRANIOCERVICAL DYSTONIA INDUCED BY OXYCODONE-ESCITALOPRAM: POSSIBLE ROLE OF GENE POLYMORPHISM AND DRUG-DRUG INTERACTIONS

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INTRODUCTION

Tardive dystonia (TD) is usually associated with long-term exposure to dopamine-receptor-blocking-agents (DRBA), but there are also nonneuroleptic compounds that are associated with TD, including antidepressants, antiepileptics, oral contraceptives, stimulants, mood stabilizers etc. Chronic pain syndromes are common in patients with depression, and clinicians frequently prescribe opioids and SSRIs together. However, coadministration of these drugs increase the risk for drug-drug interactions (Feng et al. 2017, Kotlinska-Lemieszek et al. 2015). Drug-drug-interactions-induced serotonin syndrome caused by treatment with oxycodone and SSRI is widely known (Rosebraugh et al. 2011, Karunatilake and Buckley 2006, Walter et al. 2012). We report a case of tardive craniocervical dystonia induced by coadministration of escitalopram-oxycodone.

CASE DESCRIPTION

A 56-year old woman presented with involuntary movement of her face. This follows a 10-year of depression that was treated with escitalopram 10-20 mg/day and 25-year of myasthenia gravis treated with pyridostigmin 240 mg/day and prednisone 30 mg/day. Three years before admission, she was started on 10 mg slow-release oxycodone twice daily for her back pain. Several months later, she experienced abnormal movement on her oromandibular area which is exacerbated by activity or stress. On examination, she exhibited sustained spasms of eyelids, lower face, jaw, larynx, tongue protrusion, and respiratory distress with extreme stridor which lasted 3-4 minutes and typically occured several times a week. The possibility that the patient may be manifesting a medication-induced-oromandibular-tardive-dystonia (MITD) was considered, according to the DSM-5 criteria (Figure 1). The patient scored 31/40 on Abnormal Involuntary Movement Scale, and her score on the Naranjo Adverse Drug Reaction Probability scale was 8 ponts. Other conditions were excluded by brain MRI, EEG, laboratory tests, thyroid function and immunelogical tests. Genetic analysis of CYP2D6*3*4*5*6*41, CYP3A4*22 and CYP2C19*2*17 were performed by PCR method on the Gene Amp PCR System 9700 (Applied Biosystems) to idetify gene variants potentially responsible for altered metabolism. The patient was a carrier of inactivating alleles for CYP2D6 *1/*4 and CYP2C19 *1/*2 predisposing for intermediate metabolizer phenotype. When potential side effect was identified, oxycodone was discontinued, which led to an alleviation of the symptoms 7 days later. The patient has experienced a few mild dystonic-attacks over the next 12-months of follow-up. The recomendation was given to avoid future use of oxycodone and to use antidepressants which is not CYP2D6 and CYP2C19 substrate, if needed.

DISCUSSION

This patient experienced MITD when oxycodone was coadministered to escitalopram. Concomitant use of oxycodon and SSRI has been reported to increase risk for serotonin syndrome. Dystonia has not been listed as a side effect within product information for oxycodone when given with SSRIs. We proposed several factors influencing the problem with the coadministration of oxycodone and escitalopram that may influence the development of tardive dystonia:

- The first influencing factor is ability of oxycodone to increase serotonin release, by suppressing GABA-mediated inhibition and increasing activity of serotonergic neurons. It appears that excessive binding of serotonin to 5-HT2A and 5-HT1A receptors are the pathways most likely to result in the symptoms described. This drug interaction has been supported

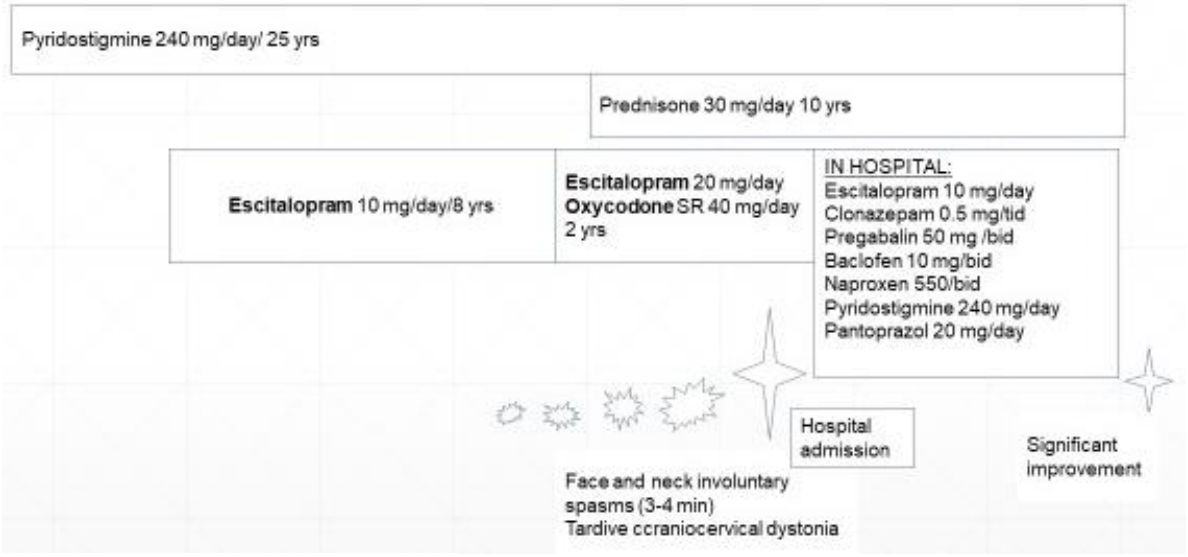

Figure 1. Patchways of oxycodone metabolism

by several case reports where serotonin syndrome has developped in patients receiving both oxycodone with sertraline (Rosebraugh et al. 2011), fluvoxamine (Karunatilake & Buckley 2006) and citalopram (Walter et al. 2012).

- The second factor is the plasma concentration of oxycodon and escitalopram, and their metabolites. Oxycodone is normally metabolized by CYP3A4 to noroxycodone and by CYP2D6 to oxymorphone. In our patient, biotransformation of noroxycodone by CYP2D6 to noroxymorphone was impaired due to inactive 2D6*4 variant. Biotransformation of escitalopram is mediated mainly by CYP3A4 and CYP2C19, with an additional contribution of CYP2D6 enzyme. Due to 2D6*4 and 2C19*2 alleles, patient had prolonged citalopram bioavailability.
- The third factor that we have proposed is the drug-drug interaction between oxycodone and escitalopram. This is supported by published case of increased oxycodone toxicity in a patient with impaired CYP2D6 metabolism (Foster et al. 2007). The potency of escitalopram to inhibit CYP2D6 enzyme activity is relatively weak compared with the other SSRIs, implying that additinal mechanisms are involved in the drug interactions in the presented cyse. Therefore, if there were any implication, it would result in less of the active metabolite oxymorphone production and in increased noroxycodone level.

Unlike oxymorphone and most opioids having affinity for the μ-opioid receptors, oxycodone shows significant affinity for κ-opioid receptors (Mercadante 2015). Opioid receptors regulate the mesolimbic-dopaminergic neurons that are located in the midbrain ventral-tegmental-area (VTA) and project to forebrain limbic structures; the ventral striatum [or nucleus accumbens (NAc)] and prefrontal cortex (PFC). Acute effects of opioids rely on opioid-induced disinhibition on dopaminergic neurons through the activation of μ-opioid receptors expressed by GABAergic interneurons located mainly in the VTA and NAc (Matsui et al. 2014). Conversely, decreased DA signaling was hypothesized to be responsible for the encoding of κ-opioid receptors-mediated aversion.

It has been hypothesized that increased serotonin levels might inhibit striatal neurons and produce an antidopaminergic effect similar to DRBAs (Albayrak & Ekinci 2012). Furthermore, D2/D3 receptors in the NAc may represent a final target of the chronic antidepressant treatment. Accordingly, it is of interest to emphasize that serotonin may influence dopamine function in the NAc through glutamatergic afferents that project to the NAc from the hippocampus, amygdala, and prefrontal cortex, the most important site of SSRI activity. Additionally, our patient received pyridostigmin and corticosteroids to treat myasthenia gravis. It is widely known that synthetic corticosteroids induced dramatic neuronal damage in the in the hippocampus and striatum. The striatal cholinergic system has been implicated in the pathophysiology of movement disorders (Calabresi et al. 2014).

CONCLUSION

Predispositions for TD existed in patient with inactivating gene-variants due to prolonged bioavailability of oxycodone, noroxycodone and escitalopram which enlarged their interacting potential. Drug-drug interactions result in higher impact of oxycodone for κ-opioid receptors, which in addition to an excess of acetylcholine in the basal ganglia indirect-pathway, may precipitate craniocervical dystonia. Pharmacogenetics may encourage personalized therapy by identifying patients at increased risk of developing side effects due to drug-drug interactions of opioid analgesics with SSRI that are CYP inhibitors, which can add to the severity of tardive dystonias.

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Iva Šarac: conception, writing the first draft, manuscript preparation, execution.

Helena Šarac: conception, organization, manuscript preparation, analysis, design.

Neven Henigsberg: analysis, review and critique.

Fran Borovečki: organization, review and critique.

Nada Božina: conception, design, manuscript preparation.

Hanna Pašić: design, analysis.

Jadranka Sertić: conception, organization, review and critique.

Zdravko Krešić: organization, analysis.

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