

Serotonin syndrome associated with methadone and milk thistle seeds: a case report

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Abstract

Background: Serotonin syndrome is rarely, potentially life threatening condition, associated with use of serotonin acting medications and psychoactive drugs. In the majority of cases the symptoms occur soon after the initiation of a new drug or a change in the dose. **Objective:** To present a case report and to describe the possible mechanism of development of serotonin syndrome during the interactions between milk thistle seeds and methadone on hepatic cytochrome enzyme system P450. **Methods:** A case report of a young man on regular therapy with methadone, who develop a serotonin syndrome after ingestion a high dose of milk thistle seeds. **Results:** Commercial preparations of milk thistle include the extract silibinin, which exhibits no beneficial or harmful drug interactions at normal doses, but at higher concentrations it can lead to dose-dependent effects on methadone metabolism, through inhibition of CYP3A4 and P-glycoprotein. As a result, it may lead to enhanced serotonin re-uptake inhibition and increased serotonin activity. **Discussion:** Milk thistle is widely used and recommended for detoxification, but it may have serious and life threatening interactions with psychotropic drugs and psychoactive substances when used in high doses.

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Keywords: Serotonin syndrome, milk thistle, silymarin, methadone, interaction, cytochrome P450.

Introduction

Serotonin syndrome (SS) is a rare, potentially life threatening, condition, associated with the use of serotonin-acting medications and psychoactive drugs. The mechanism of the formation of SS is via postsynaptic hyperstimulation of 5-hydroxytryptamine (5-HT) 2A and 1A serotonin receptors in the central and peripheral nervous system. In the majority of cases the symptoms occur soon after the initiation of a new drug or a change in the dose. The classic triad of symptoms are: altered mental status (confusion, excitement, agitation, hallucinations), autonomic dysfunction (tachycardia, tachypnea, fever, diaphoresis) and neuromuscular abnormalities (tremor, hyperreflexia, clonus, myoclonus). SS is usually self-limited once the inciting drug has been discontinued^{1,2}.

Case report

A 51-years old male with psychoactive substance use disorder, who was on methadone substitution therapy (200 mg daily) for 15 years, was admitted to a psychiatric unit for confusion and fluctuating levels of agitation. Before the admission he had been observed at the emergency department after experiencing restlessness, palpitations, dyspnea and resting tremor in the last 24 hours. ECG, laboratory tests and physical examination did not show any abnormalities, except high blood pressure (200/120 mmHg), and tachycardia and tachypnea. He admitted using milk thistle seeds regularly for some time, but in the last three days he took a full fist of seeds daily in an attempt to “detoxify” his liver because of regular alcohol consumption. At the emergency department he was disoriented, confused and agitated, with hallucinations and he was consequently transferred to the psychiatric ward. Upon admission he was still confused, with high blood pressure and tachycardia. Restlessness, hallucinations and neuromuscular symptoms (tremor of the hands and jaw, myoclonus, hyperreflexia) were also observed. Alcohol and drug screening-tests were negative. Supportive measures and a sedative agents were introduced (lorazepam 2.5 mg). After three hours, the symptoms resolved completely.

Discussion

A possible mechanism of the development of SS was through interaction on the hepatic drug-metabolizing enzyme system cytochrome P450. Methadone is a serotonin re-uptake inhibitor, metabolized by cytochrome P450, mostly by CYP3A4³. *In vitro* studies of methadone show a greater tendency toward serotonin reuptake inhibition compared with other opiates, which may explain methadone-mediated precipitation of SS⁴. Milk thistle is widely used for several medical conditions, especially for liver diseases. Commercial preparations of milk thistle include the extract silymarin, consisting of various flavonolignans, including silibinin, which have been shown to inhibit the *in vitro* activity of several cytochrome P450 enzymes including CYP3A4⁵. Silibinin exhibits no harmful drug interactions at normal doses (200-900 mg/day), but at higher concentrations it can lead to clinical important drug-drug interactions through inhibition of CYP3A4 and P-glycoprotein⁶. Results from *in vitro* studies on rats have indicated dose-dependent effects of silibinin on methadone metabolism, resulting in 50 to 100 percent reduction in methadone metabolism, which can lead to enhanced serotonin re-uptake inhibition and increased serotonin activity^{7,8}.

Conclusion

The interactions between milk thistle seeds and methadone need further investigations and more attention is recommended in patients on long-term methadone therapy using milk thistle to treat liver diseases.

Conflict of interest

Nothing to declare.

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