

Case Report

Serotonin Syndrome Developing Immediately after the Initiation of Low-Dose Methadone Therapy: A Case Report

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Keywords

Serotonin syndrome · Methadone · Oxycodone

Abstract

We present a case in which serotonin syndrome developed immediately after the initiation of low-dose methadone following an increase in oxycodone dose and the initiation of duloxetine. The symptoms of serotonin syndrome were alleviated and later disappeared upon cessation of methadone alone. The case was a 47-year-old woman with a desmoid tumor. The administration of duloxetine (20 mg/day) was initiated while the patient took oxycodone sustained-release tablets (40 mg/day). The following day, excessive perspiration, chills, and tremors appeared after the initiation of 15 mg/day methadone. Discontinuation of methadone led to an alleviation of the symptoms which completely disappeared 3 days later. The results suggest that low-dose methadone can trigger serotonin syndrome as early as after the first dose. Thus, it is important to be aware of the risks and to immediately take action if symptoms appear.

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Introduction

Serotonin syndrome (SS) is an adverse event triggered by the use of molecules such as selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors and causes some symptoms such as excessive perspiration, clonus, and tremors due to

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excessive serotonin in the central nervous system [1]. In recent years, opioids including methadone have been reported to have an inhibitory effect on the serotonin transporter (SERT), a factor that plays an important role in the reuptake of serotonin in the nerve endings [2, 3]. In 2016, the United States Food and Drug Administration (FDA) released a Drug Safety Communication to warn the medical community of the SS risk that is secondary to opioid use [4].

Herein, we present a case in which SS developed immediately after the initiation of low-dose methadone following an increase in oxycodone dose and initiation of duloxetine. The symptoms of SS were alleviated and later disappeared upon the cessation of methadone alone.

Case Report

The patient was a 47-year-old Japanese woman who noticed a mass in her left neck; MRI revealed a tumor that had deeply invaded beyond the deep cervical fascia. A biopsy revealed a pathological diagnosis of a desmoid tumor 10 months before this hospital admission. Five months prior to the admission, the patient was treated with anti-estrogen and nonsteroidal anti-inflammatory agents; however, the treatment was discontinued due to severe dizziness. Radiotherapy was initiated 3 months prior to this hospital admission, but the tumor showed no evidence of shrinkage. The patient was therefore admitted to the hospital for additional pharmacotherapy.

The chief complaints during this hospitalization were pain accompanied by allodynia on the left cervical skin and numbness of the left arm. The drugs administered at the time of admission included oxycodone sustained-release tablets 20 mg/day, oxycodone immediate-release powder (5 mg as needed for pain), pregabalin capsules 100 mg/day, and esomeprazole capsules 20 mg/day.

On hospitalization day 1, the dose of oxycodone sustained-release tablets was increased to 40 mg/day and celecoxib tablets 200 mg/day were initiated due to extreme pain. On hospitalization day 2, pregabalin capsules were discontinued and duloxetine capsules 20 mg/day (once a day in the morning after the meal) were initiated. Because nausea was observed, the administration of prochlorperazine tablets 15 mg/day was initiated together with magnesium oxide tablets 2 g/day to prevent constipation. On hospitalization day 3, duloxetine administration was changed to after the evening meal from the next day due to complaints of sleepiness and lightheadedness. Furthermore, on hospitalization day 3, methadone therapy was initiated with the intent to continue oxycodone until methadone levels reached the target concentration in serum; oxycodone would then be discontinued and a course of methadone 15 mg/day (5 mg thrice a day) would be initiated. Following the initial dose of methadone (5 mg) at 13:00 h and a second dose at 20:00 h, chills, tremors, and excessive perspiration were observed at 22:00 h. Because these symptoms repeatedly disappeared and then returned, methadone was discontinued. On hospitalization day 4, chills and tremors disappeared but there was excessive perspiration, although it improved to some degree. Excessive perspiration continued throughout hospitalization day 5 and finally disappeared on day 6. SS diagnosis was made as per the Sternbach diagnostic criteria [5]. Specifically, chills, tremors, and excessive perspiration appeared and disappeared in conjunction with the initiation and discontinuation of methadone therapy. In addition, the patient did not receive antipsychotic drug therapy or experience any change in the therapeutic regimen; infection, metabolic disorder, and/or withdrawal following substance abuse were ruled out.

Discussion

Methadone has an inhibitory effect on SERT [2, 3]. Methadone administration is categorized as an intermediate risk factor for SS according to a study by Baldo and Rose [2]. In addition, a Drug Safety Communication released by the FDA in 2016 covering cases of opioid-related SS in the FDA Adverse Event Reporting System database from 1969 through 2013 included 5 cases secondary to methadone and 7 cases secondary to oxycodone [4].

SS resulting from the combined use of duloxetine and methadone, as in the present case, has previously been reported [6]. However, this earlier report described SS secondary to multiple years of methadone, duloxetine, and desipramine use, and the patient had a methadone overdose. There are other reports on SS involving the combined use of methadone with other drugs [7–9], but in most cases the additional causative drug was administered over a long period of time and methadone was administered at high doses. We did not find any report describing the onset of SS immediately after initiating methadone at a minimum dose, as described in the present case.

Our case involved an increase in the oxycodone dose and initiation of duloxetine followed by methadone over a brief period of time. SS is likely to occur soon after the initiation of the drug [10]; polypharmacy is also a known risk factor [11]. In the present case, we cannot say for certain that methadone alone was the inciting factor; however, SS improved and eventually disappeared after the discontinuation of methadone alone while duloxetine and oxycodone were continued at the same dose. This result suggests that methadone was an important trigger in developing SS in our patient.

The incidence of SS is low; however, if the disease becomes serious, it can be life-threatening. SS presents with a variety of symptoms, and to make a definitive diagnosis can take a considerable amount of time. Of note, the package insert of methadone in the United States and Japan does not list SS. The findings of the present case suggest that physicians and patients alike should be aware of developing a risk of SS immediately following the initiation of low-dose methadone therapy and take action immediately when symptoms appear to prevent a worsening of the disease.

Statement of Ethics

This case report was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained in writing from the patient for the publication of the clinical data.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Masayoshi Kumai treated the patient, designed the research study, drafted the manuscript, and contributed to the interpretation of data. Yosuke Maeda, Mototsugu Miura, and Kenkichi Tsuruga treated the patient, revised the manuscript, and contributed to the interpretation of data. Yoh Takekuma and Takehiro Yamada revised the manuscript and contributed to the interpretation of data. Mitsuru Sugawara supervised the entire project and completed the article. All authors have read and approved the final manuscript.

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