

Restless Leg Syndrome Induced by an Acute Withdrawal of Oxycodone

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Restless leg syndrome (RLS) can develop secondary to various medical conditions. Some medications, as well as some opioid withdrawal, are known to induce RLS. Opioids modulate the dopamine system via their receptors and change the sensitivity to dopamine. Abrupt withdrawal of opioid may cause an endogenous opioid deficit state and disturb the dopamine system, which can lead to a transient dopamine dysfunctional state such as RLS. We reported a man with secondary RLS after acute withdrawal of the opioid, oxycodone, which has not been previously reported.

Sleep Med Res 2015;6(2):84-86

Key Words Secondary restless leg syndrome, Oxycodone, Opioid, Dopamine.

INTRODUCTION

Restless leg syndrome (RLS) is a common movement disorder, which disturbs sleep and consequently results in reduced daytime functioning. Alteration in nigral iron deposition and dysfunction of dopaminergic modulation is generally thought to be the main underlying pathophysiology of RLS.¹

Oxycodone, a semisynthetic opioid, is one of the treatment options for severe RLS. Its analgesic effect is mediated by κ -opioid receptor or μ -opioid receptor which is not clearly identified yet.² Oxycodone shares many common pharmacological mechanisms with other opioids. There are some reports that abrupt withdrawal of some opioids can induce RLS. Therefore, abrupt withdrawal of oxycodone is expected to induce RLS. However, RLS has never been reported as a withdrawal symptom of oxycodone.

We reported a case of secondary RLS, which developed after abrupt withdrawal of oxycodone in a patient with hepatocellular carcinoma associated with severe abdominal pain.

CASE REPORT

A 42-year-old Korean male visited the Department of Oncology due to severe abdominal pain that was caused by hepatocellular carcinoma rupture with hemoperitoneum. Lipidolol and gelfoam embolization was done at the right hepatic artery, but he still suffered from severe abdominal pain. He was treated with an analgesic (oxycodone 60 mg/naloxone 30 mg complex bid) for 10 weeks. Thereafter, abdominal pain subsided and he stopped taking oxycodone/naloxone complex at his own discretion. One week later, he developed an uncomfortable and tickling sensation on the entire body, which was particularly severe on both legs at night. This uncomfortable sensation started in the evening and gradually worsened until midnight. The symptoms were aggravated especially at rest and could be relieved only on moving or massaging his legs. Consequently, he suffered from severe insomnia and visited the Department of Neurology. His symptoms met the diagnostic criteria for RLS published by the Inter-

Received: June 24, 2015
Revised: August 9, 2015
Accepted: September 25, 2015

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national RLS Study Group.³ There was no previous history of neurologic disease and family history of RLS. In addition to oxycodone/naloxone complex, he was taking tenofovir disoproxil fumarate, ursodeoxycholic acid, silymarin, sorafenib, megestrol acetate, and metoclopramide for managing hepatocellular carcinoma. His ferritin level increased to 524.0 ng/mL possibly due to acute inflammatory reaction of hemoperitoneum. Hemoglobin, iron and total-iron binding capacity was within normal limit. His nerve conduction study also showed no significant abnormality. Neurological examination was normal.

We diagnosed oxycodone withdrawal-induced RLS and prescribed pramipexole 0.375 mg qhs and pregabalin 225 mg qhs. However, there was no improvement in the uncomfortable sensation. The dosage of pramipexole and pregabalin were increased up to 1.5 mg qhs and 300 mg qhs, respectively, and tramadol 50 mg was added at night. At that time, the severe abdominal pain recurred and he restarted taking oxycodone/naloxone complex by himself. The irresistible and uncomfortable sensations on both legs dramatically subsided. So he did not take the prescribed medications for RLS.

DISCUSSION

Several diseases can mimic RLS, but most of them do not fulfill the 4 cardinal features of RLS.⁴ In our case, all 4 cardinal features of RLS were present. He had no family history or previous history of RLS. His RLS symptoms began shortly after the abrupt discontinuation of oxycodone treatment, and the RLS symptoms disappeared soon after retaking oxycodone. There were no other neurologic deficits, abnormal laboratory finding, and abnormal nerve conduction finding that could produce RLS symptoms. None of the other drugs taken by our patient is known to induce RLS, hence, RLS was likely to be induced by abrupt withdrawal of oxycodone.

There are some reports that RLS is induced as a withdrawal symptom of some opioids such as methadone, heroin, fentanyl, and tramadol.^{5,6} In addition, many withdrawal symptoms of oxycodone such as agitation, anxiety, and sleep apnea are consistent with those of other opioids. Therefore, it is expected that oxycodone that has common pharmacological mechanism with other opioids, can induce RLS as an acute withdrawal symptom.

Evidence suggests that opioid action is linked to the dopaminergic system. Animal studies have showed that opioid may regulate the mesolimbic dopaminergic neuronal activities.⁷ Especially, μ -opioid receptor agonist may increase extracellular dopamine concentration in the nucleus accumbens that is thought to be the main regulator of oxycodone.⁷ Long-term use of opioid such as oxycodone may increase the endogenous dopamine and result in decreased sensitivity of the dopamine receptor. Thus, abrupt withdrawal of opioid such as oxycodone may reduce dopamine concentration in mesolimbic structures and

consequently produce sensorimotor problems such as RLS. One study demonstrated that morphine withdrawal decreases spine density of the nucleus accumbens, and thereby reduces dopamine transmission.⁸

The association between opioid withdrawal and RLS could be due to another mechanism. The positive response to opioid treatment for RLS suggests that decrement or hypofunction of the endogenous opioid could be another pathophysiology of RLS. One study showed that when naloxone was given to the opioid-treated RLS patients, their motor and sensory signs and symptoms returned in a qualitative and quantitative fashion, suggesting that the opioid effects on RLS symptoms are specific to the opioid receptor and implicate the role of endogenous opioid system in the pathogenesis of RLS.⁹ Recently, a post-mortem pilot study in RLS patients showed a reduction of beta-endorphin and Met-enkephalin positive cells in thalamus, which is responsible for sensory relay.¹⁰ However, dopamine activity was normal in that study. These findings are indicative of an opioid deficiency in opioid withdrawal-induced RLS patients independent of the dopamine system. In our patient, dopamine agonist did not relieve the symptoms. The RLS symptoms subsided only after taking oxycodone/naloxone complex again. Therefore, the theory above might explain the failure of dopamine agonist for relieving RLS symptoms induced by oxycodone withdrawal.

In conclusion, abrupt withdrawal of oxycodone treatment may induce secondary RLS. Clinicians should be aware of the possibility of RLS development when oxycodone is abruptly discontinued.

Conflicts of Interest

The authors have no financial conflicts of interest.

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