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Case Report

Tramadol-related psychosis in a patient with bipolar I disorder

Chen K-J, Lu M-L, Shen WW. Tramadol-related psychosis in a patient with bipolar I disorder.

Introduction: Tramadol hydrochloride (HCl) is a centrally acting synthetic opioid analgesic. Psychotic symptoms are relatively rare in reported adverse events. Here, we report a patient who presented with tramadol-related psychotic symptoms.
Case: A 59-year-old female had underlying bipolar I disorder and received lithium treatment with stable affective status. 1 month before hospitalisation, she had been taking tramadol HCl/acetaminophen for joint pain. She then developed obvious persecutory delusion. However, her clinical picture did not meet the criteria of any mood episode. After treatment of risperidone in addition to lithium, she was discharged without any psychotic symptom. She remained euthymic without any psychotic symptom on monotherapy of lithium (300 mg) three tablets once daily.
Conclusions: Tramadol HCl is commonly prescribed in clinical practice and psychotic symptoms related to it are uncommon. We should be careful about the rare but important adverse events while prescribing tramadol HCl.

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Introduction

Tramadol hydrochloride (HCl)/acetaminophen in tablet formulation has a combination of two analgesics, tramadol 37.5 mg and acetaminophen 325 mg. It is indicated for the short-term management of acute pain (1). Common psychiatric adverse events of this combined drug include anorexia, anxiety, confusion, euphoria, insomnia, nervousness, and somnolence. We are presenting a case in a patient who developed psychosis secondary to the use of tramadol HCl/acetaminophen.

Case report

This 59-year-old female bipolar I disorder patient was admitted due to delusion of persecution. She denied any history of either medical condition or substance abuse. She began to visit psychiatry clinics for depressed mood when she was 44-years old. Her depressive symptoms got improved under the daily treatment with fluoxetine 20 mg. At the age of 48 years, she had first psychiatric hospitalisation. Her clinical presentations included irritability, grandiosity, decreased need of sleep, and increased goal-directed activities. Under the diagnosis of bipolar I disorder, manic episode, fluoxetine was switched to lithium (300 mg) one tablet three times a day and haloperidol (10 mg) one tablet at bedtime. After being discharged, she had received only lithium (400 mg) varying from one tablet to two tablets once daily with euthymic mood but without psychotic symptoms.

The patient had second hospitalisation at her age of 57 years when she showed symptoms of decreased need of sleep and buying spree. She was diagnosed with bipolar I disorder, manic episode, and discharged on lithium (400 mg) two tablets once daily and olanzapine (5 mg) two tablets at bedtime.

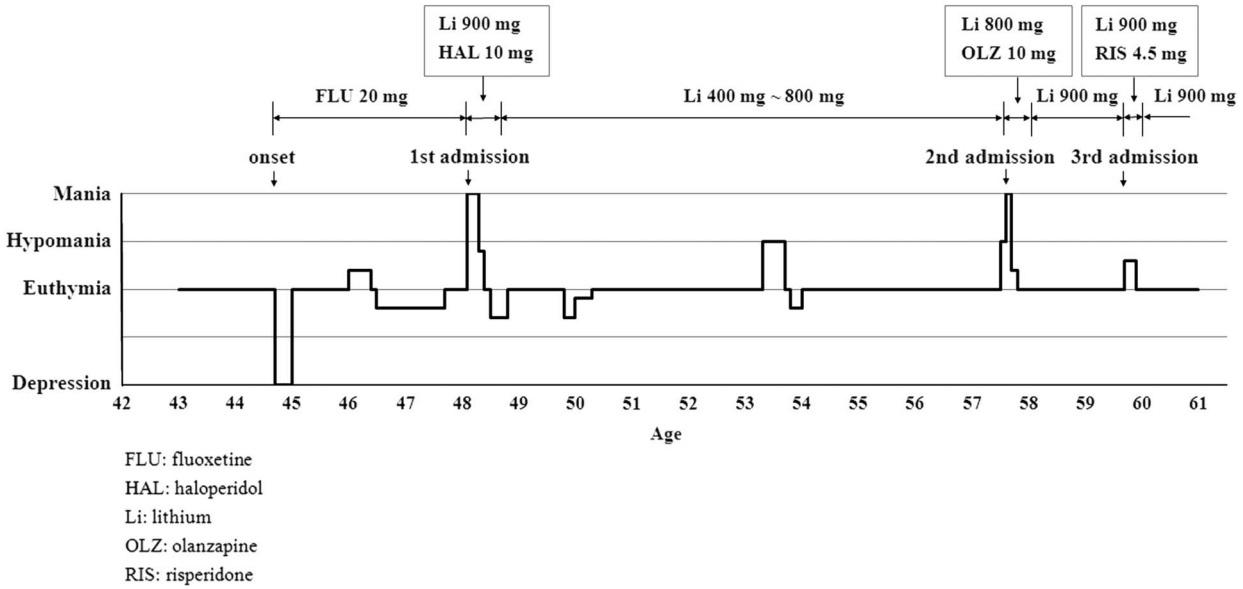

Fig. 1. Patient's clinical course and associated treatment.

Olanzapine was gradually tapered down and discontinued in 6 months. She has been on lithium (300 mg) three tablets once daily with stable mood but without psychotic symptoms until this hospitalisation.

One month before this admission, the patient began to take tramadol HCl/acetaminophen one tablet three times a day for joint pain. In the meantime, there was no newly prescribed medication other than tramadol HCl/acetaminophen. Then, she developed obvious persecutory delusion, believing that her husband and brother both attempted to take all her fortune away, resulting in having hostility towards her family members. She denied any hallucination. Moreover, her clinical picture did not meet the criteria for manic, hypomanic, or major depressive episode. She had intact consciousness level and stable vital signs. She did not have any fever, tachycardia, or neuromuscular abnormality. There is no other opioid receptor agonist side effect. Owing to obvious delusion, we treated her with quetiapine (100 mg) two tablets at bedtime and lithium (300 mg) three tablets once daily for 2 weeks. Since the third week of her admission, we switched quetiapine to risperidone owing to ongoing delusion. Two weeks after the prescription of risperidone, she was discharged on lithium (300 mg) three tablets once daily and risperidone (3 mg) 1.5 tablets once daily with euthymic mood but without any delusion. At the clinic follow-ups after discharge, we gradually tapered off and finally discontinued risperidone in 2 months because of absence of psychotic symptoms.

The patient had continued for 2 years to enjoy her good remission while receiving lithium (300 mg) three tablets once daily. The clinical course of her disorder and associated treatment is presented as a lifetime chart (Fig. 1).

Discussion

Tramadol HCl/acetaminophen consists of two ingredients. Psychiatric adverse events are rarely reported in acetaminophen (2). The other ingredient, tramadol HCl, is a weak opioid with effects on serotonergic and adrenergic neurotransmission (3). It is reported to have fewer opioid adverse effects than conventional opioid analgesia (4). The reported psychiatric adverse effects of tramadol include anxiety, confusion, coordination disturbance, euphoria, nervousness, sleep disorder, amnesia, cognitive dysfunction, depression, difficulty in concentration, hallucination, paraesthesia, seizure, and tremor (5). Persecutory delusion, in addition to auditory and visual hallucinations, secondary to tramadol use has been reported in one patient (6). The mechanism of tramadol-induced psychosis is yet unclear. However, inhibition on *N*-methyl-D-aspartate (NMDA) receptors may be an explanation. Tramadol binds to μ-opioid receptors and inhibits reuptake of monoamines in the central nervous system (7). These actions primarily contribute to its antinociceptive effects. Little is known about actions of tramadol on other receptors. One study found tramadol and its M1 metabolite (*O*-desmethyl-tramadol) significantly inhibited NMDA receptors in a concentration-dependent manner (8). The NMDA receptor hypofunction could be a potentially important component of the pathophysiology of psychosis (9).

In previous study, tramadol HCl is also reported to cause hallucinations owing to drug–drug interaction with concomitant use of flu vaccine (10). In our patient, we need to consider the possibility of drug–drug interaction-related psychotic symptoms other than direct effect of tramadol HCl. Tramadol HCl and

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lithium are both known to be associated with serotonin syndrome (11). Serotonin syndrome is the consequence of excess serotonergic activity and presented as a clinical triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities (11). Radomski et al. (12) published revised diagnostic criteria for serotonin syndrome and classified it into three main groups. One of them is mild state of serotonin-related symptoms when patients present themselves with only a single serotonin-related symptom. Mild form of serotonin syndrome owing to drug–drug interaction between tramadol HCl and lithium is also considered in our patient.

Our patient discontinued tramadol HCl after her being hospitalised, but the psychotic symptoms got remitted after a 1-month hospitalisation. The mechanism is yet unclear about the prolonged psychotic symptoms induced by a substance. Further investigation is needed for clarification. However, our patient has provided valuable clinical information on patient's safety when receiving tramadol HCl.

Clinical implications of this case

Many psychotropic agents, including antidepressant and anticonvulsant, are known to associate with serotonin syndrome. Psychiatric patients on these agents are thus vulnerable to serotonin syndrome. If these patients need pain control, physicians may first consider analgesics of mechanism different from tramadol to avoid possibility of serotonin syndrome emergence. If the patients do not respond to other analgesics and tramadol is the medication of choice, physician should be aware of the possible adverse events of psychotic symptoms, whether arise from the medicine itself or the drug–drug interaction with other medicines.

Conclusion

Tramadol HCl is commonly used in clinical practice for short-term management of acute pain. Psychotic symptoms as adverse events are relatively rare in previous reports. While prescribing tramadol HCl, physicians should pay more attention to the possible psychotic symptoms.

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Conflicts of Interest

None.

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