Post-Injection Delirium/Sedation Syndrome: A Case Report and 2-Year Follow-Up

Patient: Male, 30-year-old
Final Diagnosis: Post-injection delirium/sedation syndrome
Symptoms: Akathisia • ataxia • delirium • dysarthria • dystonia • hypertension • sedation • tachycardia
Medication: —
Clinical Procedure: —
Specialty: Psychiatry

Objective: Unusual or unexpected effect of treatment
Background: Long-acting injectable (LAI) antipsychotics are one of the forms of therapy for severe mental illness. Post-injection delirium/sedation syndrome (PDSS) is a very rare but serious adverse effect following the application of an olanzapine in a long-acting form. The most common symptoms of the syndrome are sedation, delirium, dysarthria, ataxia, extrapyramidal symptoms, agitation, dizziness, or seizure. The predispositions, prevention, and exact mechanism of PDSS remain unclear.

Case Report: We present a case report of a 30-year-old male patient experiencing PDSS, including the main symptoms of PDSS, diagnostic methods, olanzapine plasma concentrations, therapeutic process, and outcome. We then include a follow-up of the patient 2.5 years later. The patient did not have any long-term damage, had no disabilities, and no post-traumatic stress disorder following the event. We include information about his current medications, further use of LAI antipsychotics, and update about his everyday life.

Conclusions: PDSS is a life-threatening condition clinicians must be aware of, and the easiest precaution is a 3-h observation after the application of an injection. Because the predispositions, prevention, and exact mechanism of PDSS remains unclear, it is very important to report the rare cases of PDSS and conduct further research for the safety of our patients. The follow-up of the patient showed that the patient is doing well, he has no post-traumatic stress disorder following the event, and he did continue to use LAI antipsychotic medication.

Keywords: Drug-Related Side Effects and Adverse Reactions • Olanzapine • Schizophrenia

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/937579
Background

Long-acting injectable (LAI) antipsychotics are one of the forms of therapy of patients with schizophrenia. They lower the possibility of a relapse [1], prevent from hospitalization [2], and lower the risk of death [3]. Olanzapine LAI contains a pamoate salt of olanzapine and it is injected intramuscularly once every 2-4 weeks. The olanzapine pamoate is a crystalline salt composed of olanzapine and pamoic acid. After being injected into the muscle, olanzapine pamoate slowly dissolves into those compounds, which continuously enter the blood stream to achieve a steady plasma concentration of olanzapine reported to be 5-73 ng/ml [4] or 19-62 ng/ml [5] in a 405-mg dose once every 4 weeks.

Post-injection delirium/sedation syndrome (PDSS) is a very rare and possibly serious adverse effect following the application of an olanzapine LAI. The main symptoms include sedation (ranging from a somnolence to a coma), delirium, dysthria, ataxia, extrapyramidal symptoms, agitation, dizziness, or seizure [6]. In this article we present a case of a patient experiencing PDSS, including the main symptoms of PDSS, diagnostic methods, olanzapine plasma concentrations, therapeutic process, and outcome. We then did a follow-up of the patient 2.5 years later to assess the effect the PDSS event had on his mental state, to check his current medications, and to get an update on his everyday life.

Case Report

A 30-year-old White man, BMI 23.4 kg/m², was admitted to the Psychiatric Department in October 2019 for confusion and agitation with aggression. He was previously treated for paranoid schizophrenia (F20.0 based on ICD-10 classification), he was a postgraduate student, with a history of cannabis abuse and experimental use of psychedelics but abstaining for more than 6 years. In the past he was treated with risperidone and paliperidone, after which he showed extrapyramidal symptoms as an adverse effect. He was currently being treated with 405 mg olanzapine LAI once every 4 weeks, and he was taking valproic acid 1500 mg/day. We have confirmed that an olanzapine LAI was applied approximately 4 h before being admitted to the hospital; in total it was the fifth administration of the injection. The previous 4 injections of olanzapine LAI were without any problems or adverse effects. We were also informed that the patient had left the waiting room unattended after the injection.

The patient was progressively losing consciousness, became delirious, and dysarthric, and more neurological extrapyramidal symptoms occurred, including myoclonic jerks of both upper and lower limbs, akathisia, dystonia, and ataxia. He had hypertension, tachycardia, normal body temperature, and urinary incontinence. We considered a differential diagnosis of acute medication intoxication, acute intoxication with psychoactive substances, neuroleptic malignant syndrome, and PDSS. Blood tests initially showed only mild leukocytosis, slightly lowered platelet count, and very mildly lowered urea, but no other pathology. Electrocardiography showed sinus tachycardia with a possible block of a right Tawara branch. A computed tomography scan of the brain showed no acute pathology.

The patient was transferred to an intensive care unit, where a toxicology screening was performed 7 h after administration of olanzapine LAI. The plasma concentration of valproic acid was 36.0 mg/l and the olanzapine was 836 ng/ml (Figure 1), which was significantly above the laboratory alert level, which is 150 ng/ml [7]. He did not use any oral olanzapine at the time, he did not show any signs of suicidal activity, and he had not attempted suicide in the past, so accidental or intentional overdose with oral olanzapine was ruled out. We confirmed a diagnosis of PDSS based on a very high olanzapine plasma concentration and clinical symptoms of the patient. The patient was treated only symptomatically with anesthetics and benzodiazepines. Two days after the PDSS event he was fully conscious, oriented, and somatically stable. In the days after the event, he had a transient fever that was treated with antipyretics, he had intermittently mild tachycardia, and blood tests showed elevated creatine kinase, myoglobin, bilirubin, and C-reactive protein, and mild hypokalemia. In the following days, all of the symptoms gradually disappeared, and blood results normalized.

The olanzapine plasma concentration was checked again 24 h after administration of olanzapine LAI and showed a level of 93.8 ng/ml (Figure 1), which was slightly above the therapeutic concentration of olanzapine. On the sixth day after administration of olanzapine LAI, the plasma concentration was 54.4 ng/ml (Figure 1), which was in the average-steady state concentration for 405 mg/4-week dose olanzapine LAI [5].

The patient was treated with a combination of an oral olanzapine and an oral aripiprazole to be able to continue with LAI antipsychotics, but with a possibility to switch to an aripiprazole LAI. The patient was discharged from the hospital in a stable somatic and mental state with an oral medication of valproic acid 1500 mg/day, olanzapine 10 mg/day, and aripiprazole 30 mg/day.

We did a follow-up on the patient in April 2022, which is 2.5 years after the event. The patient is well compensated and visits his psychiatrist regularly. Immediately after the PDSS event, he wanted to continue with the olanzapine LAI himself, but his relatives were reluctant. His medication was therefore switched to an aripiprazole LAI, which he has continued on,
and also uses oral olanzapine and cariprazine. According to his outpatient psychiatrist, aripiprazole LAI helps him gain insight into the illness, and he has better compliance with treatment. Because he was intermittently still having some positive symptoms such as paranoia and delusional interpretation of reality, oral olanzapine was added to the treatment. Cariprazine was added because of negative symptoms. He did not have any long-term damage and has no disabilities after the PDSS event. He is continuing the LAI antipsychotic therapy and also takes oral olanzapine, and he has had no post-traumatic stress disorders following the event. Regarding his personal life, he now lives on his own, working as an academic and a researcher in the forestry industry, continuing his postgraduate studies, and just finished a 2-month internship abroad.

**Discussion**

According to the product information summary of olanzapine LAI, short- and long-term adverse effects specific to olanzapine LAI include sedation, injection site-related adverse effects, and PDSS [8]. Other adverse effects are similar to an oral olanzapine adverse effect and most frequently include somnolence, weight gain, orthostatic hypotension, elevated prolactin, cholesterol and glucose levels, dizziness, and akathisia [8]. Although the exact mechanism of PDSS remains unclear, it is presumed that it happens when the olanzapine pamoate accidentally enters the bloodstream [4] despite use of appropriate injection technique, since olanzapine pamoate has a substantially greater solubility in blood than in muscle tissue [4]. The symptoms are identical to an oral olanzapine overdose [6]. Other LAIs accidental intravascular entry would manifest in a different set of symptoms depending on the LAIs formulation and safety profile of the medication being injected [6]. PDSS is a very rare condition and occurs in 0.07% of applications in 1.4% of patients [6]. Predispositions to PDSS are unclear. It has been assumed that it more frequently occurs in patients with lower BMI and in elderly patients [6]. However, a study has disproved the relation between PDSS and lower BMI; on the contrary, it showed that PDSS more frequently occurs in patients with higher olanzapine dose (405 mg) LAI and in male patients [9], which would also be the case with our patient. Onset of PDSS occurs generally within 3 h after the injection of olanzapine pamoate, and in 91% of cases it occurs within 1 h [10], but a case of delayed onset PDSS with time-to-onset of 12 h has been reported recently [11]. Suggested treatment of patients with PDSS is symptomatic, and full recovery is achieved within 72 h. It is important to note that PDSS is not a contraindication to continue the olanzapine LAI therapy [6] as it can occur after any olanzapine LAI administration [6]. Communication with the patient is key, and it is necessary to communicate clearly and sensitively about what happened and try to minimize the possibility of developing a post-traumatic stress disorder following the PDSS event, but also to prevent future non-compliance with LAI therapy. The prevention of PDSS events remains unknown.

**Conclusions**

PDSS is a very rare and possibly life-threatening adverse event following administration of an olanzapine LAI. It can occur after any olanzapine LAI administration throughout the treatment; therefore, it is important to be aware of its existence and observe the patient for 3 h after the administration, in accordance with the product information summary [8], as occurred in this case when the patient left the waiting room unattended. The prevention of PDSS remains unknown. It is very important to report the rare cases of PDSS and conduct further research on its predispositions, possible causes, and mechanism for the safety of our patients. The follow-up of the patient shows that the patient had no post-traumatic stress disorder following the event, no long-term disabilities, and he continued to take his LAI antipsychotic medication.
Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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