Case Report

Postinjection Delirium/Sedation Syndrome with Olanzapine Depot Injection

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ABSTRACT

After 1 year of introduction of olanzapine long-acting injectable (LAI) in India, many psychiatrists believe that it is a very affordable, well-tolerated, and effective second generation long-acting antipsychotic depot compared to not well tolerated but cheap first generation antipsychotic depots and to other second generation depots which are costly. However, reports of its possible adverse events in clinical settings are not yet published. We report what probably might be the first case of postinjection delirium/sedation syndrome (PDSS) in India. Although the occurrence is uncommon, incorrect understanding of this event may hinder the future use of the potentially useful olanzapine LAI. We review the available literature on the proposed diagnostic guidelines, mechanism of this event, precautions, and management of PDSS.

Key words: *Adverse events, long-acting injection, olanzapine pamoate, postinjection delirium/sedation syndrome, schizophrenia*

INTRODUCTION

One of the greatest challenges in treating patients with schizophrenia is maintaining adherence to treatment. Poor compliance with treatment significantly increases the risk of relapse and indicates a poorer outcome.[1,2] Studies show noncompliance ranging between 40% and 60%.[3,4] Lack of insight in psychotic patients, drug side effects, lack of understanding about the illness and treatment in families are some of the factors responsible for noncompliance.

One of the solutions offered for noncompliance is long-acting injectables (LAIs). These require less active participation from patient's side, forgetting or skipping doses can be avoided, and steady plasma levels of drugs can be maintained and may allow immediate identification of nonadherence. Studies show the fewer chances of hospitalizations in patients who are on LAI compared to those who are on oral medication.[5] Since the 1960s, the first generation antipsychotic LAI are available and are widely used. These are now largely replaced by the second generation antipsychotic (SGA) LAI due to the latter's better tolerability. After risperidone, the other SGAs such as paliperidone, aripiprazole, and olanzapine LAI are now available.

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Olanzapine pamoate is the most affordable SGA LAI made available since September 2015 in the Indian market, with its efficacy being comparable to the previously marketed LAIs. It is proven to be effective in patients with schizophrenia in both acute and stable phases.[6,7] The efficacy and side effect profile of olanzapine pamoate are similar to the oral olanzapine except for the risk of injection site reaction and postinjection delirium/sedation syndrome (PDSS).[8,9]

PDSS is an uncommon and unique adverse event occuring after the injection of olanzapine pamoate which is not seen with any other long-acting injections.[10] The incidence of PDSS is seen in approximately 0.05–0.07% of injections and 0.75–1.4% of patients.[11-13] Here we present a case of PDSS and discuss various clinically important aspects.

CASE REPORT

A 32-year-old female patient presented with 2 years duration of continuous illness characterized by delusions of persecution and reference, auditory hallucinations, disturbed biological functions, and socioccupational dysfunction.

She was diagnosed as paranoid schizophrenia and was started on oral antipsychotics. However, she had a history of poor drug compliance which led to the decision to switch her to an LAI. She was started on olanzapine LAI while she was admitted in the hospital. After that she was asked to come for monthly reviews when olanzapine LAI 300 mg would be given and vitals monitored for 3 h in the hospital. She received seven injections (300 mg once every 4 weeks) without any adverse events. She showed a reduction of hallucinations, amelioration in her delusions, and improvement in the biological and socioccupational functioning.

However, on receiving the 8th injection of olanzapine LAI within 20 min, she started complaining of difficulty in walking. Before receiving the injection, she was fully conscious and well oriented. Over the next 10 min, she became extremely drowsy. She was responding with difficulty to verbal stimuli and responded with the opening of eyes for painful stimuli. She was also restless and was moving constantly. When aroused with painful stimuli, she appeared confused and spoke irrelevantly. Hallucinatory behavior related to probable visual hallucinations was present, as she was picking in the air. On The Richmond Agitation–Sedation Scale her score was - 3 (which is, moderate sedation-any movement or any eye opening to voice).

Her vitals were checked immediately after giving injection and after the appearance of the above-mentioned symptoms. Except for tachycardia (120/min), no significant changes were recorded. Tachycardia was not constant throughout the course. A thorough medical workup was done by the in-charge physician to rule out other medical causes of acute confusional state/delirium. Her blood sugars were normal (GRBS 128 mg%). Serum electrolytes and electrocardiogram were within normal limits.

In the absence of any prior medical comorbidity and the absence of any other causative agent like other drugs or infection and based on the temporal association with the injection, post-olanzapine delirium/sedation syndrome was suspected. She was kept under close monitoring and supportive care with intravenous (IV) fluids was given. Vitals (heart rate, blood pressure, and temperature) were checked half-hourly, and blood sugars (GRBS) were checked once every 3 h.

Symptoms showed resolution after 10 h. When assessed at the end of 15 h, The Richmond Agitation–Sedation Scale scoring was zero (which is - Alert and Calm). Mini-Mental State Examinations was performed after 18 h resulted in the score of 17/29 and after 36 h of 27/29. She was discharged after 36 h. Assessment on the 5th day showed that she had maintained improvement after discharge. We discussed with the patient and the caregiver and decided to continue treatment with olanzapine LAI, especially due to patient preference and due to negligible or no risk of recurrence.

DISCUSSION

The above case brings to our notice a clinically important adverse event in the treatment of patients with schizophrenia.

PDSS is characterized by the sudden and unexpected onset of delirium or sedation and their related signs and symptoms within the first several hours of receiving olanzapine LAI. In the presented case, we diagnosed this event as PDSS because of the following reasons:

- Temporal association: Symptoms developed within 20 min of olanzapine LAI
- Symptom cluster characterized by sedation, confusion, ataxia, and the presentation of the case matches the syndorme's proposed criteria[11,14]
- Absence of overdose of oral or injectable olanzapine or new exposure to olanzapine LAI
- Absence of other medical reasons for acute confusional state or sedation such as hypoglycemia, seizure, electrolyte imbalance, infection, and absence of concomitant substance use
- As known in this syndrome, she showed recovery within 18 h without any specific treatment.

According to the available literature, time of onset of PDSS ranges from 0 to 300 min after the injection and the resolution happens anywhere from 1.5 to 72 h with only supportive treatment like IV fluids. While delirium and sedation were most common signs, the other signs such as dysarthria, confusion, ataxia, and unconsciousness were also common. Nonspecific symptoms such as generalized malaise, anxiety, agitation, and irritability were also present in these patients. Vitals usually remain stable except transient and clinically nonsignificant hypertension in few patients. Although in few reports, use of antihypertensives and benzodiazepines was mentioned;[11,15] no definite management plan was advised in any of the previous studies.

Mechanism of postinjection delirium/sedation syndrome

Although initial doubts about the deficits in the manufacturing standards, reconstitution, and administration errors were thought to have caused PDSS, later investigation revealed no abnormality in production or administration of the drug. All of the PDSS patients showing raised serum olanzapine levels,[16] the similarity of the signs and symptoms of PDSS with olanzapine overdose and the resolution of the symptoms following the normalization of serum level of olanzapine indicate the accidental entry of large amounts of drug into the blood stream. Hence, it is considered to be the causative mechanism for PDSS.[15,16]

Prevention and management of postinjection delirium/sedation syndrome

There are no definite risk factors identified for PDSS, but one study[11] suggests low body mass index and advanced age as risk factors. Theoretically, factors which increase the likelihood of vessel injury such as chronic salicylate usage, alcoholism, and chronic diabetes might increase the risk of accidental drug entry into the bloodstream.[17-19] However, no studies have been conducted studying the association between these factors and PDSS.

Some guidelines to minimize the risk are advised considering the rare but potential risk of PDSS.[11,12,15] While administrating the injection, it is advised to ensure the syringe aspiration for a minimum of 5 s. If any blood is aspirated, syringe has to be discarded and a new vial should be used for reconstitution, and it should be injected into the alternate buttock. Even after this precaution as the proper injection technique alone will not completely prevent the occurrence of blood vessel injury, 3 h observation and monitoring period is mandatory after injection. It is advised to monitor mental status and vitals every half an hour during this observation period, and the patient is advised not to handle any heavy machinery or to drive the rest of the day. Psychiatrists and the nursing staff attending the patient should be trained to identify the signs of PDSS. If the patient develops any signs and symptoms of PDSS, he/she should be closely monitored until the symptoms completely resolve.

Rationale for continuing olanzapine long-acting injectable post-PDSS

It is considered safe to continue olanzapine LAI even after an event of PDSS as the case reports which followed the patients who continued to receive olanzapine LAI post-PDSS did not show any further adverse events. The previous studies which followed the patients for some months after the event reported no recurrence or any other adverse event.[15,20] However, one report[11] documents a repeat PDSS event after 6 months of the first event. It has to be noted that the patient in that report had multiple medical comorbidities such as diabetes, hypertension, chronic alcoholism, and arthritis along with the usage of analgesics.

The following graph [Figure 1] from a study[15] shows serum olanzapine levels after each LAI against the time in weeks. As depicted, when the levels reached a peak, he experienced a PDSS event and even though he continued to receive olanzapine LAI post-PDSS he did not have any further events. Benefits of improved clinical condition in the past, low incidence of movement disorders, and affordability were the deciding factors for continuing olanzapine LAI in the presented case.

The sale of olanzapine LAI has quickly caught up in the Indian market due to the faith of psychiatric practitioners on the product because of its low cost as compared to other SGA-LAIs and because of its

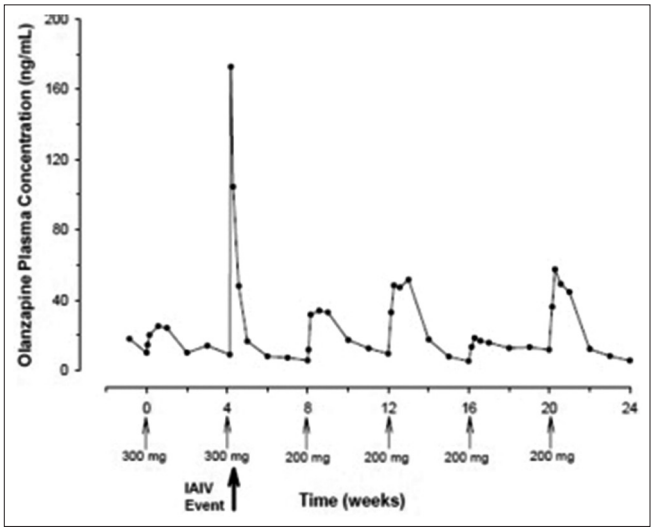

Figure 1: Serum olanzapine levels after each depot injection versus time

tolerability and effectiveness. This might mean that the knowledge of PDSS is very much required as its occurrence might not be so uncommon in the recent future. This case, to the best of our knowledge, is the first case report of "PDSS" in India. Our web search with the terms "olanzapine AND injection," "olanzapine injection," and "olanzapine AND PDSS" did not result in any relevant results in IndMED, Indian Journal of Psychiatry, and Indian Journal of Psychological Medicine.

CONCLUSION

The presented case emphasizes the importance of awareness, knowledge, and required clinical skills to identify and promptly treat the acute presentation of adverse events like PDSS in the people with schizophrenia who are on olanzapine LAI. Further prospective studies should be done with a focus on identifying risk factors and issues relating to continuation of olanzapine LAI post-PDSS.

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Conflicts of interest
There are no conflicts of interest.

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