INTRODUCTION

In patients suffering from illnesses such as schizophrenia, compliance with oral medication is found to be poor leading to relapses and subsequent hospitalization. All these indicate a poorer outcome. \(^1,2\) Some of the studies show non-compliance ranging between 40% and 60%. The factors responsible for non-compliance are lack of insight in psychotic patients, drug side effects, lack of understanding about the illness, and treatment in families. \(^3\)

Depot antipsychotics have been developed for enhancing patient compliance and improving health outcomes, possibly reducing the risk of relapses. \(^4\) Chances of hospitalizations in patients who are on long-acting injection (LAI) found to be lower compared to those who are on oral medication. The first-generation antipsychotic LAI is available since 1960 and has been used widely, now mostly replaced by the second-generation antipsychotic (SGA) LAI due to its better tolerability profile. SGA LAI such as paliperidone, aripiprazole, risperidone, and olanzapine LAI are now available. \(^3\)

In 1996 Olanzapine, an atypical antipsychotic was first introduced as an oral formulation, used in the treatment of schizophrenia and bipolar disorder. Pamoate salt of atypical antipsychotic Olanzapine in long-acting injection depot formulation (OLAI) is often used in patients with schizophrenia having poor compliance. This depot formulation having a cluster of adverse events characterized by post-injection delirium/sedation syndrome (PDSS). Here, we present three cases of different age group, different gender suffering from Schizophrenia of varied duration of illness who developed PDSS after receiving OLAI, how they were identified and promptly managed with early intervention. PDSS noted in approximately 0.07% of the injections, in 1.3% of patients. Symptoms such as sedation, delirium, extrapyramidal symptoms, ataxia, autonomic dysfunction, aggression, and speech impairment were reported, onset was immediate to 3–5 h post-injection, patients recovered within 2–72 h. No such risk factors could be identified in any of the cases. PDSS following OLAI occurs when there is accidental intravascular release of high dose of olanzapine. The importance of post-injection syndrome in the above cases lies in the fact that following administration of OLAI a 3–4-h observation period in a health-care facility in the presence of an appropriate qualified personnel is of utmost importance. Furthermore, one should rule out other causes of acute sedation in such patients before establishing the diagnosis of PDSS. There is no specific antidote for olanzapine and almost all such patients improve with conservative and supportive treatment.

Key words: Olanzapine long-acting injection; Post-injection delirium/sedation syndrome; Schizophrenia

ABSTRACT

Pamoate salt of atypical antipsychotic Olanzapine in long-acting injection depot formulation (OLAI) is often used in patients with schizophrenia having poor compliance. This depot formulation having a cluster of adverse events characterized by post-injection delirium/sedation syndrome (PDSS). Here, we present three cases of different age group, different gender suffering from Schizophrenia of varied duration of illness who developed PDSS after receiving OLAI, how they were identified and promptly managed with early intervention. PDSS noted in approximately 0.07% of the injections, in 1.3% of patients. Symptoms such as sedation, delirium, extrapyramidal symptoms, ataxia, autonomic dysfunction, aggression, and speech impairment were reported, onset was immediate to 3–5 h post-injection, patients recovered within 2–72 h. No such risk factors could be identified in any of the cases. PDSS following OLAI occurs when there is accidental intravascular release of high dose of olanzapine. The importance of post-injection syndrome in the above cases lies in the fact that following administration of OLAI a 3–4-h observation period in a health-care facility in the presence of an appropriate qualified personnel is of utmost importance. Furthermore, one should rule out other causes of acute sedation in such patients before establishing the diagnosis of PDSS. There is no specific antidote for olanzapine and almost all such patients improve with conservative and supportive treatment.

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effective in both actively psychotic as well as stable cases. This pamoate salt of Olanzapine has an elimination half-life of approximately 30 days, allowing it to be given at twice or 4-weekly interval. It 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. This OLAI, however, has a cluster of adverse events characterized by post-injection delirium/sedation syndrome (PDSS). In this study, we have reported three patients attending psychiatry department in a tertiary care hospital who presented with similar cluster of symptoms following the introduction of above-mentioned OLAI and were subsequently managed.

RESULTS

Case 1
Mr SD, 27-year-old unmarried male, underweight body mass index (BMI) (18.5) known case of paranoid schizophrenia brought by her mother to the emergency department, presented with complain of drowsiness, unsteady gait, and confusion. Two and half hours before this presentation, the patient had received his second administration of olanzapine long acting (300 mg) on that day intramuscularly at gluteal region after checking his vitals, administered by junior resident.

On examination, the patient was drowsy, orientation to time place person cannot be checked. His pulse, blood pressure, temperature, and respiratory rate were found to be normal. He was managed in psychiatric emergency observation ward, IV fluids were started, catheterization done, and vitals monitored 4 hourly.

Neurological examination showed pupil bilaterally sluggishly reacting to light and his plantar reflex was found to be extensor (Babinski sign positive). Glasgow coma scale (GCS) was E2V4M4 (10/15).

No comorbid medical/surgical illness was present. Tone and power of all four limbs found to be normal without any lateralization. No major sensory disturbances were found.

On further investigation, his blood reports for electrolytes and other parameters, brain computed tomography (CT) and brain magnetic resonance imaging, and electrocardiogram (ECG) found to be within normal limit.

After 24 h, his sensorium showed improvement, GCS started to improve, and he started to take food per mouth. After 48 h, his GCS improved become 15/15 and normal neurological examination, flexor plantar reflex, and he was discharged from the hospital.

Case 2
A 35-year-old man, overweight BMI (29.9) suffering from schizophrenia presented to our emergency department with sudden onset vertigo, hypotension (80/54 mm Hg) and impaired alertness within 45 min after his first olanzapine 210 mg IM injection in gluteal region. Airway was preserved; there was normal oxygen saturation with spontaneous breathing and patient found to be hemodynamically stable. Following his presentation, the likely diagnosis thought was an allergic reaction, so the patient was managed with an antihistaminic and fluid resuscitation. On neurological examination, GCS was 12/15; pupils had a normal size and reacting to light with cranial nerves function intact, but bilateral Babinski sign presents which found to be persist until 36 h after the admission. Other tendon reflexes were found to be normal with no extrapyramidal signs. All investigations were done including blood parameters, ECG, and brain CT and did not show any abnormalities. Twenty-four hours after his presentation, the patient became alert, cooperative, following commands (GCS 15/15) with bilateral Babinski reflex persisting. The patient was discharged with normal neurological examination after 36 h and was lost to follow-up.

Case 3
A 49-year-old married, normal BMI (24) women, known case of paranoid schizophrenia with poor compliance presented to our emergency unit with complaints of agitation, inappropriate behavior, and inability to communicate with others. She had received his fifth dose of OLAI (405 mg) through IM route in gluteal region on outpatient department basis, 4 h before this presentation. Her orientation could not be checked, blood pressure, temperature, pulse, respiratory rate, and oxygen saturation remained normal. Due to her agitation, she was initially managed with lorazepam 4 mg resulting in decrease agitation and drowsy, only reacting to painful stimuli. On neurological examination, GCS was 12/15; pupils had a normal size and reacting to light with cranial nerves function intact, and reflexes and tone and power of all four limbs were within normal limit with no extrapyramidal signs noted. Blood reports including brood toxicology screening along with brain CT, ECG electroencephalogram yielded no abnormalities. After 36 h of this presentation, the patient became alert, responsive, and obeying commands, hence discharged with normal neurological examination. She came back for follow-up after a month but despite much assurance from our side refused to continue olanzapine LAI. She was switched to oral olanzapine which she continued without any side effect.

DISCUSSION

The above three cases show us the clinical importance of adverse events in the management of schizophrenia.
OLAI though safe and effective in acute and maintenance treatment of schizophrenia but there are a few reports of PDSS, a serious adverse event of OLAI therapy. Thirty cases of PDSS were diagnosed in participants of OLAI clinical trials conducted between 2000 and 2008; almost 45,000 injections were given to 2054 patients between the ages 18 and 75 years. PDSS was noted in 1.4% of the patients (0.07% of injection). Isolated cases have been reported by Kane et al., Duran-Sindreu et al., and Buts and Van Hecke and Vodovar et al.

In the above cases, we made a diagnosis of PDSS on the basis of the following criteria:

1. Onset of symptoms – symptoms developed within 5 h of olanzapine LAI
2. Group of symptoms characterized by sedation, confusion, and the other features which matches with the syndrome’s proposed criteria
3. Absence of signs of oral olanzapine overdose and presence of new exposure to olanzapine LAI
4. Medical causes of acute confusional state such as CVA, head injury, hypo/hyper glycemia, seizure, electrolyte imbalance, metabolic, infection, and absence of comorbid substance use have been ruled out
5. Patients showing almost complete recovery within 24 h without any specific intervention.

Time of onset of PDSS varies from 0 to 5 h after the Olanzapine LAI injection and the resolution happens anywhere from 1.5 to 72 h with only conservative management. The patients manifested both neurological and vegetative symptoms, such as sedation, dizziness, confusion, delirium, slurred speech, ataxia, and muscle rigidity. Non-specific symptoms such as generalized malaise, anxiety, agitation, and irritability were also found in some cases. Although vitals remained mostly stable but transient and clinically non-significant tachycardia, hypertension occurred in few patients. A very high serum olanzapine concentrations, sometimes exceeding 600 ng/mL, was detected in some cases. Regarding management, in some cases, anti-hypertensives and benzodiazepines were used but till now no definite plan of management was mentioned in any of the previous studies.

What is the mechanism of PDSS?
Initially, many factors were thought to be responsible for PDSS like defect in manufacturing, reconstitution, and administration errors but investigations revealed no such abnormality. McDonnell et al., in 2010, found that excessive concentrations of olanzapine in the hours immediately after the injection and the signs and symptoms of PDSS found to be similar with olanzapine overdose which resolves on normalization of serum level. Maximum olanzapine concentrations during the event did not appear to correlate with dose and it has been found that PDSS events have occurred after doses of 195–405 mg olanzapine LAI doses. Studies have revealed that large amount of olanzapine could be rapidly dissolved even if only a portion of the olanzapine LAI dose were accidentally injected into a blood vessel or if the needle accidentally nicked or pierced a proximal vessel during the injection process, providing a track to access the bloodstream. This inadvertent vascular injection is the most likely explanation for the temporal and clinical symptoms of PDSS.

How to predict PDSS and prevent it?
Till now, no particular patient or medical factors have been identified which might predict PDSS except that those experiencing the syndrome are more likely to have a history of previous injection site related adverse effects. Some studies have found low BMI and/or higher age to be a risk factor for PDSS. Furthermore, conditions which increase the chance of vessel injury such as chronic salicylate usage, alcoholism, and chronic diabetes might increase the chance of drug entry into the bloodstream. However, this association still remains to be explored in further studies. The OLAI dose and concurrent therapy with other drugs do not seem to increase the risk of the syndrome.

To prevent, this rare but potential adverse effect some guidelines are advised. While administrating, the injection syringe should be aspirated for a minimum of 5s. If any blood is aspirated, syringe has to be discarded and a new vial should be used for reconstitution. It should be then injected into the alternate buttock. After injection, patients should be observed in health care facility by qualified personnel for at least 3 h for the signs and symptoms consistent with olanzapine overdose. His vitals and mental status should be ideally assessed every half an hour and if any overdose is suspected close medical supervision should continue for more than 3 h until the signs and symptoms resolve. The patient should be educated about signs and symptoms of post-injection adverse reaction and advised not to operate heavy machinery and drive for the rest of the day.

Should one continue OLAI even after PDSS?
The monitoring requirement has definitely decreased the popularity of OLAI to some extent. Most people refuse to go for OLAI following PDSS episode, but studies have revealed that it is safe to continue OLAI even after an event of PDSS. Case reports which followed the patients who received OLAI post-PDSS did not show any further similar adverse events.

There are very few studies in India that has given such a comprehensive view on PDSS following olanzapine OLAI. Our study is unique in that aspect. PDSS is a rare but potentially risky phenomenon and the knowledge about its
signs, symptoms, and management techniques should be well informed among the psychiatrists as well as nursing staffs to diminish panic among the patients and relatives.

**CONCLUSION**

The above cases emphasize on the importance of knowledge among health care personnel regarding the exact nature of these post-injection syndrome, what signs and symptoms to look for in their patients during what time frame, and also what to expect in terms of clinical progression, management, and outcomes following the development of such an event after Olanzapine LAI in patients of Schizophrenia. Further studies should be conducted on this topic of PDSS following OLAI to clear our concepts.

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**REFERENCES**


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