Case Series Profile of Olanzapine Post-Injection Delitrium/Sedation Syndrome

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Abstract

Olanzapine pamoate is an intramuscular depot injection for the treatment of schizophrenia. Approximately 1.4% of patients develop a serious adverse event called Post Injection Delirium/Sedation Syndrome (PDSS); characterised by drowsiness, anticholinergic and extrapyramidal symptoms. The objective is to investigate olanzapine PDSS presentations including clinical features and treatment approach. This is a retrospective review of olanzapine PDSS patients from three toxicology units and the NSW Poisons Information between 2017 and 2022. Adult patients were included if they had intramuscular olanzapine then developed PDSS criteria. Clinical symptoms, treatment, timing and length of symptoms were extracted into a preformatted Excel database. There were 18 patients included in the series, with a median age of 49 years (IQR: 38-58) and male predominance (89%). Median onset time post injection was 30 minutes (IQR: 11-38). PDSS symptoms predominate with drowsiness, confusion and dysarthria. Median length of symptoms was 24 hours (IQR: 20-54). Most common treatment included supportive care without any pharmacological intervention (n=10), benzodiazepine (n=4) and benztropine (n=3). In one case, bromocriptine and physostigmine followed by oral rivastigmine were given to manage anti-dopaminergic and anti-cholinergic symptoms respectively. This proposed treatment combination could alleviate some of the symptoms. In conclusion, this case series supports the characterisation of PDSS symptomology predominantly being anti-cholinergic with similar onset (<1 hour) and duration (<72hours). A combination of bromocriptine and physostigmine followed by rivastigmine is proposed to manage PDSS if patients develop severe dopamine blockade or anti-cholinergic delirium.

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Introduction: Olanzapine is a new generation of thienobenzodiazepine class antipsychotic that has antagonist effect on serotonin (5-HT_{2A}, 5-HT_{2C}), dopamine (D_1, D_2, D3, D_4), histamine (H_1), α_1-adrenergic and muscarinic receptors. Olanzapine pamoate is a long-acting salt based intra-muscular depot injection for the treatment of schizophrenia since 2009[1]. From 2000-2008, It is observed that Delirium/Sedation Syndrome (PDSS) occurred approximately in 0.07% of injections or 1.4% of patients who underwent clinical trials to assess the safety of olanzapine long-acting injection (LAI)[2]. In this cohort, PDSS is characterised by excessive sedation, delirium, anticholinergic symptoms, extrapyramidal symptoms, dysarthria or ataxia within an hour of injection[2]. The theorised pathophysiology is partial intravascular inoculation, with inappropriate rapid dissolution of the salt-based formulation due to direct exposure to the high solubility in blood rather than muscle tissue[3]. This is supported by the fact that PDSS is primarily reported amongst patients who received olanzapine palmoate depot injection and not other long acting injectables[4]. In addition, the syndrome's presentation with anticholinergic and anti-dopaminergic symptoms is similar to oral olanzapine overdose and high serum olanzapine levels occur in those who develop it[5, 6]. Current management for this condition is limited and involves supportive care and benzodiazepines for agitation[7]. We aimed to investigate characteristics of olanzapine PDSS including onset, clinical features and treatment approach.

Methods: This is a retrospective review of patients who were diagnosed with olanzapine PDSS from South-eastern Sydney toxicology unit in New South Wales, Calvary Mater Newcastle toxicology unit in New South Wales, Princess Alexandra Hospital toxicology unit in Queensland and the New South Wales Poisons Information Centre between January 2017 and February 2022. Adult patients over 18 years old were included if they had been given intramuscular olanzapine and then developed symptomology whilst fulfilling PDSS criteria outlined by Detke[2](Table 1).

Patient demographics, clinical symptoms, time to symptoms, length of symptomology and treatment were extracted and entered in a preformatted Excel database. Categorical variables are summarised in percentages, with skewed numerical data in median and interquartile range (IQR) as appropriate. All involved institutions have ethics approval from their respective Human Research and Ethics Committees.

Results: There were 18 patients in the case series who met the inclusion criteria, with a median age of 49 years (IQR: 38-58, range: 21-38) and male predominance of 89% (n=17). The most frequent dosage given in patients with PDSS was 405mg with doses ranging from 210-405 mg. All but 2 patients had the olanzapine depot injection in the past. The median onset time to PDSS symptoms was 30 minutes (IQR 11-38, range: 5-180). PDSS symptoms predominate with drowsiness, confusion, slurred speech, agitation and ataxia as highlighted by Figure 1. However, the most frequent symptoms on presentation were drowsiness (61%), dizziness (22%) and confusion (11%). Median heart rate on arrival was 91 beats per min (bpm) (IQR: 85-115, range: 73-150). Forty-one percent (41%) of patients has tachycardia on arrival defined as heart rate greater than 100 beats per minute. Median Systolic blood pressure was 128 mm Hg (IQR 128-140, range: 70-160) and temperature 36°C (Range: 36-39). Median Glasgow Coma Scale was 13 (IQR: 10-14, range 3-15) and muscles tones were noted to be increased, some with rigidity in 4 patients. Two patients were intubated,

one following sedation with benzodiazepines. Complications included aspiration pneumonia (n=1), buttock abscess (n=1) and rhabdomyolysis (n=1). Patients in our study had a median length of symptoms of 24 hours (IQR: 20-54; range: 1.5-70h). The treatments given were supportive care (n=10), benzodiazepines for agitation (n=4), benztropine (n=3), physostigmine (n=2), rivastigmine (n=2) and bromocriptine (n=1).

One patient received both physostigmine and bromocriptine for pronounced anticholinergic and antidopaminergic toxicity. This was a 48-year-old male admitted with progressive weakness, confusion, dysarthria and rigidity 15 minutes post first depot intramuscular injection of 210mg Olanzapine, to which he received 2mg Benztropine in 1mg aliquots to minimal avail. His heart rate was 90 bpm, BP 115/85 mm Hg, temp 37.1°C. He developed anti-cholinergic toxicity with progressive agitated delirium, sinus tachycardia and urinary retention in addition to extrapyramidal signs of cogwheeling in all four limbs and tremor. This was complicated by rhabdomyolysis (peak CK 25,331 IU/L) and a mild acute kidney injury (Creatinine 117 µmol/L, baseline Creatinine 69 µmol/L). He was managed supportively with intravenous fluids and urinary catheterization. Intravenous physostigmine 2mg was administered and effectively reversed his anti-cholinergic symptoms rapidly, in particular the delirium. The patient then received oral rivastigmine 6mg three times a day for 2 days. The anti-dopaminergic symptoms (cogwheel rigidity) were then treated with bromocriptine 5mg three times a day for 6 doses. There was complete resolution of anti-dopaminergic and anti-cholinergic symptoms within 70 hours. This patient subsequently received increasing dosage of paliperidone with no adverse effects. While it is possible that neuroleptic malignant syndrome may have accounted for the rhabdomyolysis and renal impairment,[8] the rapid onset and resolution of symptoms makes this differential less likely. Rather the time course is more consistent with dopamine blockade secondary to olanzapine.

Discussion:

This retrospective case series was inclusive of 18 patients that had similar demographics with a median age of 48 years old compared to other studies[9]. There was a marked male prevalence at 89% in this study, which although increased when compared with previous studies[2, 9] is likely a representation of small sample size.

The median onset of olanzapine PDSS post injection of 30 minutes (IQR 11-38min) in our series is similar to previous studies that showed 80-90% developed symptoms within 1h[2, 9, 10]. Moreover, this rapid onset further supports the pathophysiology of PDSS of partial intravascular penetration and subsequent premature dissolution of the depot by McDonell[3].

The most common first symptom displayed post injection was drowsiness (61%) followed by dizziness (22%) and confusion (11%), which is analogous to all reported case series (Figure 1) [2, 9, 10]. These case series suggest PDSS symptomology primarily being those of anti-cholinergic syndrome. Complications like urinary retention, rhabdomyolysis and fever appear to be less frequent. Moreover, the distribution of anti-cholinergic over anti-dopaminergic symptoms mimics that of oral olanzapine overdose[5,6] adding further support to the theorised pathophysiology of PDSS being that of premature rapid dissolution of the salt intravascularly[2].

The case series revealed a median PDSS duration of 24 hours, with all patients' symptoms lasting within the 1.5-72 hour, duration noted also by previous studies[2, 9, 10]. The most common treatment was supportive care without any pharmacological treatment (56%) and benzodiazepines for agitation (22%). Olanzapine PDSS has no formal treatment to minimize the not so insignificant duration of these debilitating symptoms, aside from supportive care[2, 10]. However, in the case described we propose a treatment approach with bromocriptine and physostigmine followed by rivastigmine to manage anti-dopaminergic and anti-cholinergic symptoms respectively. Although physostigmine treatment is new in the scope of Olanzapine PDSS, it is recommended to be used to manage patients with anticholinergic delirium[11]. Rivastigmine was used following successful reversal of delirium with physostigmine due to favourable pharmacokinetics with longer duration of action (10h). Rivastigmine has been used to treat prolonged delirium in anti-cholinergic syndrome as it could reduce symptom recurrence and decrease need for re-dosing[12, 13]. Furthermore, bromocriptine was chosen as it has been suggested for the management of extrapyramidal symptoms such as rigidity and dystonia[14]. This proposed treatment as highlighted by the case may provide substantial opportunity to lessen or shorten symptoms of this adverse reaction.

Conclusions: This case series demonstrated characteristics of PDSS symptomology predominantly being those of anti-cholinergic over anti-dopaminergic symptoms with similar onset (<1 hour) and duration times (<72hours). A proposed treatment of physostigmine then rivastigmine for anti-cholinergic symptoms and bromocriptine for anti-dopaminergic symptoms is suggested for the management of PDSS, which may provide significant possibility to reduce symptoms.

Declaration of interests: The authors report no declarations of interest.

Table 1. Clinical Criteria for the diagnosis of PDSS following olanzapine long-acting injection (LAI)[2].

1. One or both of the conditions listed in (a) and (b): (a)A minimum of 1 sign or symptom of moderate severity from at lea
2. Signs and symptoms develop within 24 hours of an olanzapine LAI.
3. Condition cannot be explained by a significant dose increase of olanzapine LAI or other medications.
4. Other medical conditions including drug use have been ruled out.

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`Figure 1. PDSS symptoms.docx` available at https://authorea.com/users/505902/articles/584831-case-series-profile-of-olanzapine-post-injection-delitrium-sedation-syndrome