mhc MENTAL HEALTH CLINICIAN

CASE REPORT Open Access

Postinjection delirium/sedation syndrome in a transgender man undergoing hormone therapy

Joshua Gerving, PharmD, BCPS, BCPP[1]
Heather Walser, PharmD, BCPP[2]
Anne C. Kelly, MD[3]

How to cite: Gerving J, Walser H, Kelly AC. Postinjection delirium/sedation syndrome in a transgender man undergoing hormone therapy. Ment Health Clin [Internet]. 2022;12(4):263-6. DOI: 10.9740/mhc.2022.08.263.

Submitted for Publication: April 20, 2022; **Accepted for Publication:** July 13, 2022

Abstract

Background: Long-acting injectable medications have become an important tool in the treatment of schizophrenia and schizoaffective disorder due to the high rates of medication nonadherence. Olanzapine long-acting injection (OLAI) is a useful therapeutic option for patients who have good tolerability and efficacy to oral olanzapine. Postinjection delirium/sedation syndrome (PDSS) is a rare but potentially serious event with the proposed mechanism of inadvertent intravascular injection of OLAI. This concern necessitates the requirement of a 3-hour monitoring period postinjection. Based on a literature review, there are no clearly defined risk factors for developing PDSS.

Case Report: A case is presented that describes PDSS in a transgender man undergoing hormone therapy with testosterone. The patient received OLAI for more than 3 years and developed PDSS 9 months after the initiation of injectable testosterone.

Discussion: There are published case reports of PDSS with the use of OLAI; however, there are no documented cases in a patient undergoing concurrent testosterone therapy. The effect that testosterone has on the vascular system and how it may alter the pharmacokinetics of OLAI has not been studied.

Conclusion: Despite proper injection technique, PDSS can occur after injection with OLAI. Further research is necessary to identify specific risk factors for the development of PDSS, including the potential effect that hormone therapy may have.

Keywords: antipsychotic agents, drug-related side effects and adverse reactions, schizophrenia, olanzapine, transgender, hormonal therapy, testosterone

[1] (Corresponding author) Clinical Pharmacy Specialist, Boise Veterans Affairs Medical Center, Boise, Idaho, joshua.gerving@va.gov, ORCID: https://orcid.org/0000-0001-8737-2605; [2] Clinical Pharmacy Specialist, Boise Veterans Affairs Medical Center, Boise, Idaho, ORCID: https://orcid.org/0000-0001-9322-2048; [3] Psychiatrist, Boise Veterans Affairs Medical Center, Boise, Idaho, ORCID: https://orcid.org/0000-0003-3626-3681

Disclosures: The authors have no relevant financial or nonfinancial relationships to disclose.

Background

Medication nonadherence is challenging in patients with schizophrenia and schizoaffective disorder and is associated with higher rates of relapse and rehospitalizations with poorer outcomes.[1-4] The use of long-acting or depot therapies has become common in psychiatric practice to address nonadherence to oral pharmacotherapy.[3-5] The World Federation of Societies of Biological Psychiatry

guideline recommends long-acting injectables when the "avoidance of covert nonadherence with antipsychotic drugs is a clinical priority."[6(p4)]

Olanzapine long-acting injection (OLAI) is an IM depot formulation with a similar safety profile to oral olanzapine with exception of postinjection delirium/sedation syndrome (PDSS).[3,5,7] PDSS is an adverse reaction unique to OLAI that is categorized by sedation, confusion, slurred speech, altered gait, or unconsciousness.[5] The incidence of PDSS is studied to be as low as 0.044% of the total number of injections given (about 1.17% of patients).[8] The risk is the same at each injection but increases with the total number of injections.[3,5,8] Repeat incidences are also documented in the same individual.[8]

The exact mechanism of PDSS is unknown but is likely the result of unintended partial intravascular injection, resulting in supratherapeutic blood concentrations of olanzapine with blood concentrations reported as high as 670 ng/mL (reference 20 to 80 ng/mL).[4,5,9-11] Additionally, it is hypothesized that the elevated olanzapine concentrations observed during PDSS are secondary to the enhanced rate of dissolution of OLAI in blood rather than the slow medication release from the OLAI depot with repeated dosing.[5]

No clear risk factors for PDSS are identified from clinical trials. Limited evidence identifies decreased BMI and increased age as possible risk factors.[4] One observational study[8] finds higher dose per injection and male assigned sex are also risk factors, whereas another article[10] finds no correlation between dose and maximum plasma concentrations of olanzapine. Absorption and bioavailability of IM medications are also dependent on physiological factors, such as local blood flow.[12] Increased blood flow in an injection site area allows for greater absorption rate of the medication.

In 2017, the Endocrine Society released guidelines to establish a framework for endocrine treatment of transgender individuals.[13] Testosterone therapy is used to suppress endogenous hormone secretion and maintain sex hormone concentrations within the normal range for the individual's identified gender. Goal testosterone levels in the male physiologic range are 300 to 1000 ng/dL.[14] Within 3 months of initiating testosterone therapy, the following changes are expected: cessation of menses, increased facial and body hair, skin changes and increased acne, changes in fat distribution, increases in muscle mass, and increased libido.[13,15] In addition to these expected changes, the vasodilatory effect of testosterone is studied in many test subjects, including humans.[16,17]

The proposed mechanism of testosterone's vasodilatory effects is complex and not well-understood. Testosterone-induced vasodilation may be explained by its modulation of K^+ channels and/or inhibition of voltage-dependent Ca^{2+} channels.[17] Activation of K^+ channels represents the main mechanism of relaxation by causing a membrane hyperpolarization. This hyperpolarization, in turn, closes voltage-dependent Ca^{2+} channels, decreasing calcium entry into smooth muscle cells, leading to vasodilation. Testosterone may also have direct inhibitory effects on Ca^{2+} channels, which similarly reduce calcium entry into muscle cells. The resulting vasodilation can increase blood flow in those affected parts of the body.

Vasodilation can increase the surface area of each vessel for nutrient exchange and can also alter the surface area throughout the tissue in a process known as capillary recruitment.[18] Testosterone can promote neutrophil infiltration, which may increase inflammation.[16] The combination of these testosterone-induced physiologic changes and how they may alter the pharmacokinetics of OLAI has not been studied.

Case Report

A 26-year-old transgender White male, weighing 66 kg, was being treated with OLAI for schizoaffective disorder, bipolar type, with treatment refractory symptoms. Past medical history is significant for gender dysphoria, alcohol use disorder in remission, history of cannabis use in remission, and tobacco use disorder. The patient was on OLAI for more than 3 years with an initial dose of 405 mg every 4 weeks. After 9 months, the dose was changed to 405 mg every 3 weeks due to breakthrough symptoms. Six months later, he again showed symptoms refractory to this dose. He was not a candidate for oral augmentation due to a history of nonadherence. The OLAI was titrated to an off-label dose of 405 mg every 2 weeks with documentation in the medical record regarding the risks and benefits of dosing strategy, citing evidence of high-dose oral olanzapine up to 60 mg/d.[19] This dose of OLAI was considered by the treatment team to be approximately equivalent to 30 mg/d of oral olanzapine by dividing the OLAI dose per injection by the number of days in the interval as is done with approved doses of OLAI.[5] This dose provided good symptom control and tolerability for 23 months. Pertinent concomitant medications included oral gabapentin 900 mg twice daily for anxiety, mood, and alcohol cravings (with poor adherence) and nicotine gum for cravings. The nicotine gum was rarely used, and the amount of smoking was consistent throughout OLAI therapy, likely reducing fluctuations of olanzapine metabolism.

After 29 months of OLAI monotherapy, the patient elected to undergo gender transition with hormone therapy. Injectable testosterone cypionate was initiated at 50 mg IM every 2 weeks and was titrated to 80 mg every 2 weeks

after 6 months. He was on the combination of testosterone and OLAI for 9 months and was on the higher dose of testosterone for the last 3 months before the PDSS event. The 2 injections were administered on the same day in opposite gluteal sites. Serum testosterone concentrations remained therapeutic during treatment, ranging from 40 ng/dL at baseline to 450 to 600 ng/dL while on therapy.

On the day of event, he presented to the behavioral health outpatient clinic for his 68th overall injection of OLAI. The clinic was equipped with proper staffing to provide the mandatory 3-hour postinjection monitoring. Less than a minute after the olanzapine injection, he stated that he was not feeling well, complaining of leg pain and sialorrhea. He noted dizziness and quickly transitioned to laying supine on the floor. He then became somnolent, lethargic, and confused and was taken to the emergency department located on campus. The emergency department noted he had slurred speech and was difficult to arouse. A Glasgow Coma Scale performed in the emergency department had a total score of 8 (E2 V2 M4). Urine drug screen and blood alcohol concentration were negative. A blood gas study was also performed and was within normal limits. He was subsequently admitted to observation status on a telemetry unit where he remained somnolent for the next 12 hours. The next morning, 24 hours after OLAI injection, he was reported to be more alert, and his mental status continued to improve that same day to allow for discharge after an approximately 30-hour admission. Continuous cardiac monitoring and EKG were all negative for cardiac abnormalities and no medications or intravenous fluids were administered. Vital signs, liver function, and kidney function were within normal limits, whereas blood glucose concentrations ranged from 97 to 142 mg/dL. A serum olanzapine concentration drawn at 2 hours postinjection was >300 ng/mL with no baseline comparison. A repeat serum concentration drawn at 27 hours postinjection was also >300 ng/mL. On follow-up in the outpatient setting, the patient was given the option to resume OLAI, and he declined. Oral olanzapine 30 mg/d was reinitiated 14 days after the last OLAI injection when the olanzapine concentration was 70 ng/mL. Enhanced emphasis was placed on oral adherence by providing prefilled medication organizers and weekly adherence assessments via telephone calls by the treatment team.

Discussion

The potential for onset of PDSS is greatest within the first hour after injection, and most patients fully recover within 72 hours.[5,9,10] Although symptoms are generally consistent with olanzapine overdose with supratherapeutic systemic concentrations, the exact mechanism of PDSS is unknown.[9] There is insufficient data to suggest specific risk factors. The most hypothesized theory involves accidental entry of the medication into the bloodstream following blood vessel injury during the injection process. There is inconsistent evidence showing that decreased BMI, increased age, higher dose per injection, and male assigned sex may increase its risk. Increased blood flow is shown to alter the pharmacokinetics of IM medications, including long-acting antipsychotics.[12] Testosterone can cause vasodilation in human blood vessels, which can lead to increased blood flow.[17] No publications were identified regarding hormone therapy as a risk factor, and no correlation can be assumed between testosterone and the development of PDSS in our case patient. The event could have occurred regardless of testosterone therapy. Nevertheless, the physiologic changes during hormonal therapy should be considered when assessing the pharmacokinetics of IM injections.

Conclusion

PDSS is a complication that can occur after an injection of OLAI despite proper administration. Pathophysiology of this adverse event is not well-understood, and there is insufficient data to identify well-defined risk factors. Further observations and studies are necessary to form conclusions regarding hormonal therapy as a potential risk factor. PDSS reactions, although rare, continue to reinforce the requirement for OLAI postinjection monitoring.

Acknowledgments

We acknowledge Nixon VanJustice and Susan Klepacki for contributing insight into the appropriate use of inclusive language.

References

1. Lindenmayer J-P, Liu-Seifert H, Kulkarni PM, Kinon BJ, Stauffer V, Edwards SE, et al. Medication nonadherence and treatment outcome in patients with schizophrenia or schizoaffective disorder with suboptimal prior response. J Clin Psychiatry. 2009;70(7):990-6. DOI: 10.4088/JCP.08m04221. PubMed PMID: 19497244.
2. Murru A, Pacchiarotti I, Nivoli AMA, Bonnin CM, Patrizi B, Amann B, et al. Rates and clinical correlates of treatment non-adherence in schizoaffective bipolar patients. Acta Psychiatr Scand. 2012;125(5):412-8. DOI: 10.1111/j.1600-0447.2012.01837.x. PubMed PMID: 22321052.
3. Luedecke D, Schöttle D, Karow A, Lambert M, Naber D. Post-injection delirium/sedation syndrome in patients treated with olanzapine pamoate: mechanism, incidence, and management. CNS Drugs. 2015;29(1):41-6. DOI: 10.1007/s40263-014-0216-9. PubMed PMID: 25424243.
4. Venkatesan V, Khanra S, Mandal K, Deepak MB. Postinjection delirium/sedation syndrome after 31st long-acting olanzapine depot injection. Clin Neuropharmacol. 2019;42(2):64-5. DOI: 10.1097/WNF.0000000000000329. PubMed PMID: 30747749.
5. Heres S, Kraemer S, Bergstrom RF, Detke HC. Pharmacokinetics of olanzapine long-acting injection: the clinical perspective. Int Clin Psychopharmacol. 2014;29(6):299-312. DOI: 10.1097/YIC.0000000000000040. PubMed PMID: 24815672.

6. Hasan A, Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects. World J Biol Psychiatry. 2013;14(1):2-44. DOI: 10.3109/15622975.2012.739708. PubMed PMID: 23216388.
7. Kane JM, Detke HC, Naber D, Sethuraman G, Lin DY, Bergstrom RF, et al. Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. Am J Psychiatry. 2010;167(2):181-9. DOI: 10.1176/appi.ajp.2009.07081221. PubMed PMID: 20008947.
8. Meyers KJ, Upadhyaya HP, Landry JL, Chhabra-Khanna R, Falk DM, Seetharama Rao B, et al. Postinjection delirium/sedation syndrome in patients with schizophrenia receiving olanzapine long-acting injection: results from a large observational study. BJPsych Open. 2017;3(4):186-92. DOI: 10.1192/bjpo.bp.116.004382. PubMed PMID: 28811926.
9. Uglešić L, Glavina T, Lasić D, Kaliterna M. Postinjection delirium/sedation syndrome (PDSS) following olanzapine long-acting injection: a case report. Psychiatr Danub. 2017;29(1):90-1. PubMed PMID: 28291981.
10. McDonnell DP, Detke HC, Bergstrom RF, Kothare P, Johnson J, Stickelmeyer M, et al. Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection, II: investigations of mechanism. BMC Psychiatry. 2010;10:45. DOI: 10.1186/1471-244X-10-45. PubMed PMID: 20537130; PubMed Central PMCID: PMC2895590.
11. Schoretsanitis G, Kane JM, Correll CU, Marder SR, Citrome L, Newcomer JW, et al. Blood levels to optimize antipsychotic treatment in clinical practice: a joint consensus statement of the American Society of Clinical Psychopharmacology and the Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft für Neuropsychopharmakologi. J Clin Psychiatry. 2020;81(3):19cs13169. DOI: 10.4088/JCP.19cs13169. PubMed PMID: 32433836.
12. Yin J, Collier AC, Barr AM, Honer WG, Procyshyn RM. Paliperidone palmitate long-acting injectable given intramuscularly in the deltoid versus the gluteal muscle: are they therapeutically equivalent? J Clin Psychopharmacol. 2015;35(4):447-9. DOI: 10.1097/JCP.0000000000000361. PubMed PMID: 26061612.
13. Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. Endocr Pract. 2017;23(12):1437. DOI: 10.4158/1934-2403-23.12.1437. PubMed PMID: 29320642.
14. Safer JD, Tangpricha V. Care of the transgender patient. Ann Intern Med. 2019;171(1):ITC1-16. DOI: 10.7326/AITC201907020. PubMed PMID: 31261405.
15. Unger CA. Hormone therapy for transgender patients. Transl Androl Urol. 2016;5(6):877-84. DOI: 10.21037/tau.2016.09.04. PubMed PMID: 28078219; PubMed Central PMCID: PMC5182227.
16. Herring MJ, Oskui PM, Hale SL, Kloner RA. Testosterone and the cardiovascular system: a comprehensive review of the basic science literature. J Am Heart Assoc. 2013;2(4):e000271. DOI: 10.1161/JAHA.113.000271. PubMed PMID: 23842280.
17. Lorigo M, Mariana M, Lemos MC, Cairrao E. Vascular mechanisms of testosterone: the non-genomic point of view. J Steroid Biochem Mol Biol. 2020;196:105496. DOI: 10.1016/j.jsbmb.2019.105496. PubMed PMID: 31655180.
18. Kolka CM, Bergman RN. The barrier within: endothelial transport of hormones. Physiology (Bethesda). 2012;27(4):237-47. DOI: 10.1152/physiol.00012.2012. PubMed PMID: 22875454.
19. Citrome L, Kantrowitz JT. Olanzapine dosing above the licensed range is more efficacious than lower doses: fact or fiction? Expert Rev Neurother. 2009;9(7):1045-58. DOI: 10.1586/ern.09.54. PubMed PMID: 19589053.