CASE REPORT

Resolution of Retrograde Ejaculation with Three-monthly Paliperidone Palmitate: A Case Report

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Abstract

Sexual dysfunction is not uncommonly seen among patients being treated with antipsychotics. Retrograde ejaculation has been reported with the atypical antipsychotic paliperidone palmitate and it related to antagonism of the alpha-1 receptor. The author presents a case of a 27-year-old man who was admitted due to a manic relapse of his bipolar disorder. At the time, he was on quetiapine 400 mg bd. Upon stabilization, a decision was made to augment his treatment with intramuscular paliperidone palmitate for long term relapse prevention. Nine months later, his manic symptoms were under control, but he developed retrograde ejaculation. A urology consult determined that the causative agent was the monthly paliperidone palmitate and a decision was made to switch him to the three-monthly paliperidone palmitate. After two doses of the new formulation, he was able to resume having anterograde ejaculation. It is postulated that the longer time to achieve peak concentration and slower release of the three-monthly formulation are the possible reasons for the resolution of the patient's retrograde ejaculation. Switching from monthly to three-monthly formulation of paliperidone palmitate may help alleviate retrograde ejaculation in patients who are already showing remission of their illness with monthly paliperidone palmitate.

Keywords: Sexual Dysfunction, Paliperidone Palmitate, Ejaculation, Antipsychotic Agents

Background

Antipsychotic-induced sexual dysfunction, though common, is a challenging area of psychopharmacology to manage, affecting up to 75 % of patients taking antipsychotics (Kirino, 2017). Among the implicated mechanism are increase in prolactin, reduced dopaminergic activity and also alpha-1 receptor blockade(de Boer et al., 2015). Antipsychotics that raise prolactin and have higher binding affinity for alpha-1 receptors such as risperidone, amisulpiride and olanzapine, tend to have more sexual adverse effects such as erectile dysfunction, loss of libido, premature ejaculation and retrograde ejaculation(Huhn et al., 2019; Allen et al., 2019) Paliperidone palmitate is

a long acting injectable (LAI) atypical antipsychotic and it was approved by the US Food and Drug Agency (FDA) in 2009. It works as an antagonist at the D2,5HT2 and alpha-1 receptors, and has negligible antagonism at the histaminic and muscarinic receptors (Corena-McLeod, 2015). In 2015, the three-monthly paliperidone palmitate formulation was approved by the US FDA for the maintenance treatment of patients who were in remission of schizophrenia.

Retrograde ejaculation is a phenomenon whereby the usual anterograde flow of semen is redirected into the urinary bladder due to ineffective bladder sphincter contraction(Rowland et al., 2010). Several antipsychotics with potent alpha-1 blockade have been implicated in causing retrograde ejaculation, such as clozapine, olanzapine, risperidone and paliperidone palmitate (Baldwin and Mayers, 2003; Holtmann et al., 2003; Shalbafan et al., 2019; Madan et al., 2018; Loh et al., 2004). Although retrograde ejaculation is common, its literature, particularly on its association with antipsychotic usage is scarce. To the author's knowledge, this is the first case illustrating the improvement of retrograde ejaculation upon switching from monthly to three-monthly paliperidone palmitate.

Case Presentation

A 27-year-old patient with bipolar disorder type 1, was seen at the outpatient unit with complaints of gradual agitation, increase in goal directed activity and grandiose ideations. At that point in time, he was compliant on oral quetiapine 400 mg bd and lorazepam 1 mg bd for two years. In view of his impending manic relapse, a decision was made to admit him for stabilization. During his admission, his manic symptoms resolved gradually. After sessions with the patient a shared decision was made to combine oral quetiapine with paliperidone palmitate as a off-label long-term relapse prevention measure.

At baseline, he did not have any sexual dysfunction or any other contraindications to start this medication. After tolerability testing with oral paliperidone was done, a loading dose of intramuscular paliperidone palmitate 150 mg was given, followed by 100 mg eight days later. He was maintained on a dose of 100 mg monthly of the LAI and was able to remain in remission of his illness. He remained in remission while on the quetiapine 400 mg bd and monthly intramuscular paliperidone palmitate combination.

Nine months later, the patient confided to the clinician that he could not ejaculate anymore despite experiencing erection and orgasm. This was very upsetting for him and he contemplated stopping the treatment. A referral to a urologist was made at this point and an extensive physical examination and investigation was done. No abnormality was found on his examination, but his serum prolactin was within normal range at 19.1 microgram/L and serum testosterone normal at 17.4 nmol/L. A urine sample detected the presence of spermatozoa. A diagnosis of retrograde ejaculation was confirmed, and the monthly paliperidone palmitate was singled out as the causative reason. After a risk-benefit discussion with the patient, a decision was made to switch his monthly to the three-monthly paliperidone palmitate formulation, in combination with oral quetiapine. A dose equivalent conversion was made, and he was started on 350 mg of three-monthly paliperidone palmitate. After the second injection was administered, he reported improvement in his retrograde ejaculation and was able to re-experience anterograde ejaculation again. Currently, he

enjoys a normal sex life and remains in remission of his bipolar disorder.

Discussion

Sexual dysfunction is an important but often less highlighted aspect of antipsychotic usage. It can take the form of reduced libido, decreased arousal, erectile difficulties for men, sexual pain disorders and ejaculatory disorders such as premature ejaculation and retrograde ejaculation(Hatzimouratidis and Hatzichristou, 2007) It is important to address sexual dysfunction as it invariably leads to poor compliance to treatment, stigma and reduce quality of life. Retrograde ejaculation is worrying as it has been reported to contribute to infertility and is the most common cause of ejaculatory dysfunction (Zhao et al., 2004).

Postsynaptic alpha-1 receptor antagonism is linked to the reversal of ejaculate flow as it leads to relaxation of the bladder sphincter during ejaculation (Sanbe et al., 2007). It is interesting to note that oral paliperidone ER has been reported to improve risperidone related retrograde-ejaculation as it's binding affinity is three times to the alpha-1 receptor is three times lesser (Kandasamy, 2012). Paliperidone palmitate, however, has been reported to cause retrograde ejaculation(Madan et al., 2018). This difference can be explained by the varying exposure of paliperidone on the alpha-1receptor. As paliperidone ER's half-life is significantly shorter than that of paliperidone palmitate (23 hours vs 25-49 days)(Mathews et al., 2020), this translates to shorter exposure of the medication at the receptor level, thus leading to decreased likelihood of developing retrograde ejaculation.

In our case study, the patient's retrograde ejaculation improved markedly upon switching from the monthly to three monthly formulation of paliperidone palmitate. This result can be explained by analyzing the pharmacokinetics of both formulations. Three monthly paliperidone palmitate has a longer half-life compared to its monthly counterpart (84-95 days with deltoid administration,118-139 days with gluteal administration vs 25-49 days). However, it takes longer time to achieve maximum concentration (T_{max}) compared to monthly paliperidone palmitate (30-33 days vs 13 days), resulting in a more gradual exposure of the alpha-1 receptor in patients on three monthly formulation of paliperidone palmitate(Janssen Inc.,2015). Another possible explanation is that the slower release of the three monthly formulation resulted in reductions in peak-to-trough fluctuations of drug concentration, resulting in lesser propensity to develop adverse sexual side effects such as retrograde ejaculation(Siegel, 2005).

Conclusion

Clinicians need to be aware of the risk of sexual dysfunction with antipsychotic therapy, particularly retrograde ejaculation, as it may affect treatment outcomes. In patients already in remission with monthly paliperidone palmitate who develop retrograde ejaculation, switching to the three-monthly formulation may be considered. The latter's longer time to achieve peak concentration and slower release compared to the monthly formulation renders it less likely to cause retrograde ejaculation. More research is needed to further elucidate the causal relationship between various formulations of paliperidone palmitate and sexual dysfunction.

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