Paliperidone Palmitate-Induced Retrograde Ejaculation

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Introduction

Paliperidone palmitate is a long-acting intramuscular (LAI) formulation of paliperidone, an active metabolite of risperidone. While its specific mechanism of action is unknown, it is believed that paliperidone's antagonism of central dopamine Type 2 (D2) and serotonin Type 2 (5HT2A) receptors are responsible for its therapeutic actions. Paliperidone is also an antagonist at alpha 1 and alpha 2 adrenergic receptors and H1 histaminergic receptors. Paliperidone has no known affinity for cholinergic, muscarinic, or beta-adrenergic receptors (1, 2). Paliperidone palmitate was approved by the FDA in August 2009 in the acute- and maintenance-treatment phases of schizophrenia in adults (3-6). Advantages of paliperidone LAI in comparison to other long-acting injectables include once-a-month dose requirement, flexibility of dosing and a more rapid attainment of steady state concentrations. In clinical trials, most common adverse events (incidence ≥5% and occurring at least twice as often as placebo) were injection site reactions, somnolence/sedation, dizziness, akathisia and extrapyramidal disorder. Sexual side effects observed during postmarketing evaluations included amenorrhea, erectile dysfunction, galactorrhea, gynecomastia and irregular menstruation (1).

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Antipsychotic-induced sexual dysfunction is often under reported and associated with poor quality of life and a common reason for treatment nonadherence. Paliperidone palmitate's package insert lists retrograde ejaculation as a potential reproductive adverse effect. There are case reports of retrograde ejaculation and priapism with clozapine (7), risperidone (8-13) and olanzapine (7). To the best of our knowledge, there have been no published reports of retrograde ejaculation with oral paliperidone or its injectable formulation. Interestingly, there is a published report of successful use of paliperidone in a patient with oral risperidone-induced retrograde ejaculation (13).

We report a case of retrograde ejaculation following paliperidone palmitate therapy. The symptoms improved and resolved following dose reduction and eventual discontinuation of the medication.

Case Report

Mr. X, a young male in his early twenties, diagnosed with schizophrenia about three years ago, was seen for an evaluation in the outpatient clinic. The patient had an extensive history of inpatient psychiatry hospitalizations, presumably triggered by poor medication adherence. Presenting symp-

toms in the clinic included paranoid delusions, auditory hallucinations and generalized anxiety. He did not have a history of somatic delusions. Patient's medications at the time of his initial presentation included clonazepam 1 mg two times a day, hydroxyzine 10 mg three times a day and olanzapine 25 mg QHs. His past medical history was nonsignificant for any acute or chronic medical problems. Based on his symptoms and history of medication nonadherence, a decision to start him on long-acting paliperidone palmitate was made. Following the loading dose of 234 mg, he was continued on a maintenance dose of 156 mg every month. Patient was maintained on hydroxyzine; however, clonazepam and olanzapine were discontinued.

Within approximately three months of starting paliperidone palmitate, the patient began to experience erectile dysfunction and retrograde ejaculation. A trial of sildenafil did not prove helpful. The patient was very concerned with his minimal to complete lack of ejaculate even with normal libido. At times he would notice his urine to be cloudy post masturbation and orgasm. His sexual side effects would improve during the week preceding his scheduled injection of paliperidone and worsen after he received his injection. Patient had no prior history of sexual dysfunction. He did not report any prior bladder, pelvic area surgeries or history of spinal cord or nerve damage. He denied any associated symptoms such as painful micturition, burning sensation or presence of blood in urine. Routine labs—including CBC, CMP, urine routine exam, TSH and UDS—were within normal limits. Prolactin was elevated to 42.6 ng/ml (normal range 2.6–13.1 ng/ml). We did not confirm the presence of sperm in the urinalysis after orgasm. He did not experience any breast tenderness or engorgement.

Given the patient's level of distress and adverse impact on his quality of life and relational functioning from his sexual side effects, a decision to taper paliperidone palmitate was made. Oral olanzapine was reintroduced. The cross taper was done over a period of about three months. The patient reported return of normal ejaculation as we reached a dose of 39 mg/day. His psychotic and anxiety symptoms were adequately stabilized on olanzapine 30 mg. His prolactin level a month after discontinuing paliperidone palmitate injection was 29.7 ng/ml.

Discussion

Sexual dysfunction is a common side effect of treatment with antipsychotics. Despite the increasing awareness of this problem, sexual side effects often go undetected. Sexual side effects from antipsychotic medication range from diminished interest/arousal, delayed orgasm to erectile dysfunction. The resulting sexual dysfunction has potential to impair quality of life, lead to intimacy problems and adversely impact medication adherence and compliance in schizophrenia (14).

According to the *Medical Dictionary for Regulatory* Activities, the definition of retrograde ejaculation (RE) includes a broad spectrum of patient reported events of abnormal ejaculation, including absence of seminal emission, reduced ejaculate volume, and reduced ejaculation force. Common causes include surgeries of urinary bladder neck or prostate surgery, medications with alpha-blocking effect as used to treat high blood pressure, prostate enlargement, and nerve damage caused by a medical condition, such as diabetes, multiple sclerosis or a spinal cord injury. It's believed that relaxation of the bladder neck muscle secondary to alpha-receptor blockade leads to backflow of seminal fluid from the prostatic urethra into the bladder. There are several case reports of risperidone-induced retrograde ejaculation (7-12). Since paliperidone is an active metabolite of risperidone, one would anticipate a similar side effect profile, including retrograde ejaculation. Most of the other sexual side effects of risperidone and also presumably paliperidone appear to be due to a direct reflection of D2 antagonism-induced hyperprolactinemia, which results in decreased sexual function indirectly through lowering of serum testosterone levels.

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Postsynaptic antagonism of the alpha 1 adrenergic receptor has been implicated in retrograde ejaculation by altering the sympathetic tone of the bladder or urethral sphincter. To date, all drugs reported to induce retrograde ejaculation share the ability to significantly antagonize alpha 1 adrenergic receptor (8). The absence of this particular adverse effect among psychotropics that lack this specific pharmacological property affirm this hypothesis (9). There is a report where oral paliperidone was used as an alternative for oral risperidone-induced retrograde ejaculation. Since risperidone's potency for alpha 1 adrenergic receptor antagonism is three times that of paliperidone, switching to paliperiodone could, in theory, relieve retrograde ejaculation symptoms. However, our report suggests that this strategy might not work in all cases.

Antipsychotics such as paliperidone—by virtue of their dopamine blockade—can lead to sexual side effects from hyperprolactenemia and resulting hypogonadism. Although our patient had elevated prolactin levels, the lack of any arousal difficulties suggests that the retrogarde ejaculation was very likely from paliperidone's postsynaptic antagonism

of the alpha 1 adrenergic receptor rather than direct reflection of hyperprolactinemia. However, it is possible that both mechanisms contributed to the patient's symptoms.

Our case report underscores the importance of early recognition of sexual side effects in patients receiving antipsychotic medications. Retrograde ejaculation—even though rare—should be explored, especially with antipsychotics that have potent alpha 1 adrenergic antagonistic properties. Retrograde ejaculation can be frightening and potentially destabilizing for the patient. Careful history taking in an empathic and nonjudgmental manner, along with support and reassurance, is critical. We recommend basic lab work including urine analysis for semen and prolactin level. A gradual dose reduction and, if needed, cross taper to a different antipsychotic with lesser potency for the alpha 1 adrenergic receptor, should be attempted.

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